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A DIFFERENTIAL QUANTITATIVE TUBERCULIN TEST[1]

JOHN E. BLAIR AND WALTER I. GALLAND

As an accessory in the diagnosis of tuberculous infection, the tuberculin test has been the subject of considerable study, and has received varying degrees of approbation and disapproval since Koch's first description of the reaction. Acclaimed at first with enthusiasm, it later was regarded with distrust, and only in comparatively recent years has the test been found to have a definite place, when properly performed and interpreted, as an aid in establishing a diagnosis of tuberculosis.

The subject of tuberculin and the tuberculin reaction has recently been well summarized by Long (1). It has been established that the tuberculin reaction is based upon hypersensitivity of the individual. Coming under the broad heading of allergy, the reaction has been classified by Coca and Cooke (2) among the reactions described as "hypersensitivity of infection." The active principle taking part in the phenomenon has generally been considered to be of a protein nature, in spite of occasional proposals of other substances, such as protein derivatives and even protein-free compounds, as the active agent. The protein nature of tuberculin has received substantiation by several recent investigations, notably by the work of Long and Seibert, and by Seibert's success finally in crystallizing a water-soluble protein in pure form which gives a marked skin reaction in tuberculous guinea pigs (3.) In addition, hypersensitivity to tuberculin has been distinguished from tuberculin anaphylaxis, and a carbohydrate gum has been isolated which gives reactions of precipitation and complement fixation without producing any tuberculin reaction (4) (5). Explanation of the mechanism of the tuberculin reaction has reached no satisfactory conclusion.

An important feature of the tuberculin reaction from the point of view of diagnosis is its specificity. It is commonly believed to be highly specific as an indicator of the presence of tuberculous infection. It is well known that the conditions necessary for a tuberculin reaction are established by the presence of either living or dead tubercle bacilli, and the peculiar sensitivity is always associated with the presence of anatomical tubercle.

[1] From the Laboratory Division, Hospital for Joint Diseases, New York City.

It has become a trite expression to say that the tuberculin reaction indicates tuberculous infection and not tuberculous disease, but this question is of extreme importance in a consideration of diagnosis by means of tuberculin. If the presence of anatomical tubercle alone is shown by a tuberculin reaction, no information is gained as to whether the tubercle is relatively fresh, formed as a reaction to actively developing tubercle bacilli, and a potential focus for future dissemination of the disease, or whether it is densely encapsulated and has become quite innocuous.

It would appear plausible that active tuberculous disease, with continual reaction of the individual to repeated liberation of toxic material from the focus of activity, would be accompanied by a degree of hypersensitivity quite different from that found in a latent infection or a long-continued process of healing, in which the escape of toxic substance from a focus is inhibited or prevented by walling-off. Consequently, it would seem that some method of performing the tuberculin test quantitatively could differentiate between latent infection and active disease. By the administration of a series of graded dilutions of tuberculin it should be possible to establish a point, above which reactions to dilutions would be obtained only in those individuals possessing a considerable degree of hypersensitivity; that is, in persons actively combatting tuberculous disease. As pointed out by Long, "in the last analysis, the specificity of the tuberculin test will probably be found in its quantitative aspect."

Types and Modifications of Quantitative Tuberculin Tests: A: Cutaneous Tests: Attempts have been made in the past to modify the existing tuberculin tests, apparently with the purpose of bringing out a difference in sensitivity as shown by variations in reaction to a series of tuberculin dilutions. With the Pirquet test in vogue, some of the first modifications were quantitative cutaneous reactions. In 1909 Ellermann and Erlandsen (6) reported a cutaneous test in which they employed drops of 32 per cent, 8 per cent, 2 per cent and 0.5 per cent of O. T. By measuring the diameter of reacting areas, computing the mean difference between them, and estimating the diameter which might be given by a 4 per cent papule, they computed the "tuberculin titre," a mathematical statement of the degree of sensitvity of the patient. The tuberculin titre increased with an increase in the degree of tuberculous infection, a titre of 200 or over indicating active tuberculosis, and a low titre (usually under 100) accompanying latent infection. Shortly after this report came a series of cutaneous tests by White and his coworkers (7). In these

tests a 1 per cent tuberculin was employed, with an elaborate technique for its application, followed within a few days by a second test, employing a stronger or weaker dilution, depending upon the outcome of the first test. The attempt was made to determine the least amount of tuberculin which, when applied to the skin, would produce a "minimal cutaneous reaction," that is, a reaction of redness and induration of about 4-mm. diameter within 72 hours. The patient's individual sensitivity was thus determined, and the dosage for subsequent tuberculin treatment was based upon the amount of tuberculin necessary to cause a minimal cutaneous reaction.

A considerable inaccuracy is common to all cutaneous tuberculin tests, since apparent differences in reactions are generally not real, particularly when the differences amount to only a few millimetres in the diameters of the reacting areas. The cutaneous test can be of no value when used quantitatively, as it is modified by quite uncontrollable variations; for example, thickness of skin, power of absorption, loss of tuberculin by oozing of blood and depth of scarification. This point has been mentioned by numerous investigators, and was demonstrated by Boardman's study of the technical factors involved in cutaneous tests (8).

A method of differentiating between active and quiescent tuberculous lesions was proposed by Pottenger (9), who employed only the Pirquet test, without a series of dilutions. He considered as indicative of active tuberculosis a reaction which reached its maximum within 36 hours. Any reaction attaining its maximum only after 36 to 48 hours was considered as indicating latent infection. The objections to the cutaneous test cited above apply with equal force in this case.

B. Intracutaneous Tests: Of the various types of tuberculin tests used for the diagnosis of tuberculosis in human beings, the intracutaneous test is generally considered to be the most accurate. The subcutaneous test too often gives severe focal and general reactions. No constantly accurate dosage can be attained in cutaneous and percutaneous tests, and the ophthalmic test has value only in children, in whom other methods are fully as informative and less distressing.

A quantitative intracutaneous tuberculin test was used by Roemer and Joseph (10) in 1909 on a series of guinea pigs representing all grades of tuberculous infection. They found a correlation between severity of infection and reaction to the intracutaneous administration of extremely high dilutions.

Hamman and Wolman (11), and later Smith (12), have employed

intracutaneous tests in diagnosing human cases, using a series of dilutions from 1:10,000 to 1:1,000,000 and 1:10,000,000, respectively, but no statistical information is given to demonstrate the value of the method in their hands.

Opie and McPhedran (13) have made use of a quantitative intracutaneous test as an accessory in studying a large group of individuals to determine the incidence of tuberculosis and its relation to contagion. An initial dose of 0.01 mgm. of O. T. was employed. If no reaction occurred in 48 hours a second injection of 0.1 mgm. was given, followed two days later, in the event of a negative reaction, by a third dose of 1 mgm. Reactions were graded according to their severity, and the inference may be drawn that latent infection was indicated by weak reactions or reactions to only the larger amounts of tuberculin. Correlating the tuberculin reaction and the ability to recognize tuberculous lesions by roentgenological examination, it was found that "with positive reactions, increasing intensity of reaction is associated with gradually mounting frequency of recognizable tuberculous lesions." Also, "the probability of grave infection increases with the severity of the tuberculin reaction." The work has been extended by Opie and his associates to an examination of several thousand children (14). They believe that the only accurate method of determining the incidence of tuberculous infection in apparently healthy children is by means of an intracutaneous tuberculin test.

Atsatt (15) described a modification of the Mantoux intracutaneous test, which he considers to be of value in the diagnosis of bone and joint tuberculosis. The essence of his quantitative reactions consists of establishing a threshold of tuberculin sensitivity, above which threshold tuberculin allergy would warrant a presumptive diagnosis of clinically active tuberculosis, but below which threshold one might expect various degrees of tuberculin allergy to be exhibited by persons carrying latent or healed tuberculosis. Using Saranac human tuberculin, a dilution of 1:7500 was established as the threshold of reaction. The test, as he describes it, consists of administering at one session intracutaneous injections of 0.1 cc. of Saranac tuberculin in dilutions of 1:1000, 1:2500, 1:5000, 1:7500, and 1:10,000, together with a saline control. A cutaneous response to the 1:10,000 dilution is considered as being significant of the presence of clinical bone or joint tuberculosis, in the absence of other tuberculous manifestations. Atsatt reports a series of tests covering 211 cases, 85 of which were tuberculous, upon whom this quantitative reaction was performed. Considering his cases, irrespective of age-groups, 90

per cent of the nontuberculous cases gave a negative reaction, while 92 per cent of the tuberculous cases gave a positive reaction, that is, positive in the dilution of 1:10,000.

EXPERIMENTAL

Studies with Human and Bovine Tuberculin: In attempting to repeat Atsatt's work, using tuberculin generously supplied by the New York City Department of Health, we obtained conflicting results. Individuals known to be clinically nontuberculous frequently gave florid reactions to all of Atsatt's recommended dilutions, invalidating the diagnostic value of reaction to the 1:10,000 dilution. Similar results followed the use of several commercial tuberculins. Under the definite impression that the quantitative intracutaneous tuberculin test might be of value, and that the tuberculin which we used was of greater potency than that employed by Atsatt, we modified the test, employing dilutions of 1:10,000, 1:25,000, 1:50,000, 1:75,000 and 1:100,000. With this series we concluded that reactions to dilutions of O.T. of 1:25,000 or below carried no diagnostic significance, and that reaction above this dilution indicated active tuberculosis.

Using the above modification, we performed quantitative intracutaneous tests upon 144 individuals, tuberculous and nontuberculous, representing all age-groups. The results of this series of tests have been reported elsewhere (16). Briefly, our findings closely paralleled Atsatt's reported figures. Of the tuberculous cases which we tested, 91 per cent reacted to the diagnostic dilutions, while 90 per cent of the nontuberculous group gave diagnostically significant negative reactions. We are quite in accord with Atsatt's hypothesis that a critical threshold may be established, such that reactions to dilutions of O.T. above the threshold may be considered as usually indicative of active tuberculosis (in our series, 91 per cent). In a parallel series of intracutaneous tuberculin tests, using both Saranac and New York City Department of Health tuberculins, we found that the Saranac tuberculin was distinctly less potent. The difference between Atsatt's threshold and ours is thus explained. In spite of this difference, we are unable to subscribe to the performance of intracutaneous tests with dilutions as concentrated as those suggested by Atsatt. It would appear preferable to use for these tests very potent tuberculin, admitting of high dilution, thus avoiding the injection of any considerable amount of tuberculoprotein.

Upon continuing this work, we became convinced that tuberculous

individuals reacted with uniformity to far smaller amounts of tuberculin than we had been using. For the most part it was noted that in a positive test there was very little difference in intensity of the reaction produced by the dilutions from 1:25,000 to 1:100,000. Inasmuch as reaction to these intermediate dilutions yielded no more information than did the reaction to 1:100,000, we proceeded to determine the extreme dilution to which a frankly active tuberculous individual would respond. Employing dilutions of 1:1,000,000, 1:10,000,000, and 1:100,000,000 of O.T., it was found that the majority of tuberculous individuals reacted to dilutions as high as 1:10,000,000, and occasional cases reacted definitely to 1:100,000,000. Nontuberculous cases showed no response whatsoever to such infinitesimal amounts of tuberculin.

We therefore revised our technique to include the following dilutions of tuberculin: 1:10,000, 1:100,000, 1:1,000,000, and 1:10,000,000. A positive reaction to dilutions of 1:100,000 or above was considered as indicating active tuberculosis. Reaction to the 1:10,000 dilution, which is the criterion of the Mantoux test, and is the upper limit of Atsatt's series, carries, in so far as we have been able to determine, no diagnostic significance of an active lesion.

Impressed by the fact that we occasionally obtained unexplained negative responses in cases which were proved to be clinically active, we inferred that perhaps these cases were infected with the bovine type of tuberculosis. A quantity of bovine tuberculin was procured through the courtesy of Dr. E. A. Watson of the Animal Diseases Research Institute of the Department of Agriculture, Quebec. Using dilutions of this bovine tuberculin corresponding to those mentioned above, and making parallel tests with both the human and bovine series it was established conclusively that certain cases react with definitely greater intensity to either one or the other tuberculin, even to the extent that some individuals, reacting but faintly or not at all to one tuberculin, showed definite reactions to all dilutions of the other.

We have therefore concluded that any quantitative tuberculin test which aims to be usefully accurate must include parallel series with both human and bovine tuberculin. The earliest application of a differential diagnostic tuberculin test appears to have been that proposed by Detre (17). He employed the technique of the Pirquet test, using both human and bovine tuberculins. Objections to the cutaneous type of test have already been mentioned. In 1926 Downing and Higgins (18) reported a series of intracutaneous tests with human and bovine tuberculin, and

concluded that both types should be used in routine tuberculin tests. However, their intracutaneous tuberculin test was done with a dilution of 1:1000, which dilution, if made with the commercially obtainable tuberculins, we consider to be quite unsafe for administration. We have seen a frankly ulcerative lesion develop upon the site of administration of this concentration of tuberculin.

Technique of the Differential Quantitative Test: As finally adopted, the technique of the differential quantitative tuberculin test is as follows: The following dilutions of both human and bovine tuberculin are prepared: 1:10,000, 1:100,000, 1:1,000,000, and 1:10,000,000. Sterile phenol-saline (0.5 per cent phenol) is used as the diluent, and as a control in the test. The dilutions are kept on ice, and discarded at the end of one week, at which time they have always been found to be potent. Two tuberculin syringes and 26-gauge needles are used for each test, one for the human and one for the bovine series. It is essential that syringes and needles be absolutely clean and free from every trace of tuberculin. The injections are made intracutaneously, beginning with the control and proceeding from the most dilute to the most concentrated solutions. Aseptic precautions are of course used throughout the test. The injections may conveniently be made upon the forearm, the upper arm or the external aspect of the thigh. For cosmetic reasons, we have seen fit to avoid the use of the forearm as a site for the injections, particularly in women. We have found it most desirable to inject the human and bovine dilutions in parallel lines about two inches apart, with the corresponding dilutions upon the same level, so that comparison of intensity of reactions is facilitated. The results are read at the end of 24 and 48 hours, as the maximum reaction is sometimes delayed.

The criterion for a positive reaction consists of the formation of an indurated cutaneous nodule, usually, but not always, accompanied by erythema, at the site of injection. A positive reaction to dilutions of 1:100,000 and over is considered as indicative of active tuberculosis. Response to the 1:10,000 dilution, and not to any of the higher dilutions, in our experience, indicates only latent or healed tuberculosis.

RESULTS

We are reporting herein the combined results of all quantitative tuberculin tests which we have performed to date,—a total of 471. Of these, 121 cases were proved to be tuberculous, and 350 cases were finally considered to be nontuberculous. Proof of tuberculosis was established by

guinea-pig inoculations, smears, operative findings, pathological sections, or X-ray findings, and usually by a combination of two or more of these criteria. When none of these findings was positive, a case was considered as nontuberculous, regardless of a positive intracutaneous test.

In chart 1 a summary may be seen of the statistical aspects of the entire series of tests. Disregarding fractional percentages, of 121 tuberculous cases, 110, or 90 per cent, gave a diagnostically positive reaction (that is, reaction to 1:100,000 or above). The remaining 11 cases, 9 per cent, gave diagnostically negative reactions. Several of these individuals were moribund, and, as is well known, would react, if at all, only to large amounts of tuberculin. One case had been receiving a protracted course of tuberculin therapy, and was thereby immunized to the amounts of tuberculin used in the tests. Of the 11 cases, 4 reacted to only the

Explanation of Chart 1

In groups A, B and C the left-hand columns represent the tuberculous cases; the right-hand columns, the nontuberculous cases.

A. All cases studied, representing all age groups.

B. Cases 10 years of age and over.

C. Cases under 10 years of age. *Solid columns*—total number of cases. *Cross-hatched*—positive reaction to all dilutions. *Oblique lines*—positive to the 1:10,000 dilution, but not to the higher dilutions. *Blank columns*—no reaction to any dilution.

D. Cases of bone and joint tuberculosis tested with both human and bovine tuberculin. *Solid columns*—total number of cases. *Parallel horizontal lines*—definitely greater reaction to bovine tuberculin. *Parallel vertical lines*—definitely greater reaction to human tuberculin. *Stippled*—reactions of equal intensity to both human and bovine tuberculin.

1:10,000 dilution. Tuberculosis in these instances was proved by the criteria mentioned above, and they undoubtedly are individuals possessing a low degree of tuberculin allergy. It would be impossible, nevertheless, to consider the reaction to the 1:10,000 dilution in these cases as significant from the diagnostic standpoint, inasmuch as it will be pointed out later that a large proportion of clinically nontuberculous subjects respond sharply to this concentration of tuberculin.

In the group considered to be nontuberculous (350 cases), 324, or 92 per cent, gave a clinically significant negative reaction, while 26, or 7 per cent, reacted to all dilutions. We would stress the fact that, except in the period of infancy and very early childhood, the classical cutaneous tuberculin test is without value. Our findings would indicate that the Mantoux test is equally unreliable in the older individual, for, of 276 cases ten years of age or over, giving a diagnostically significant negative

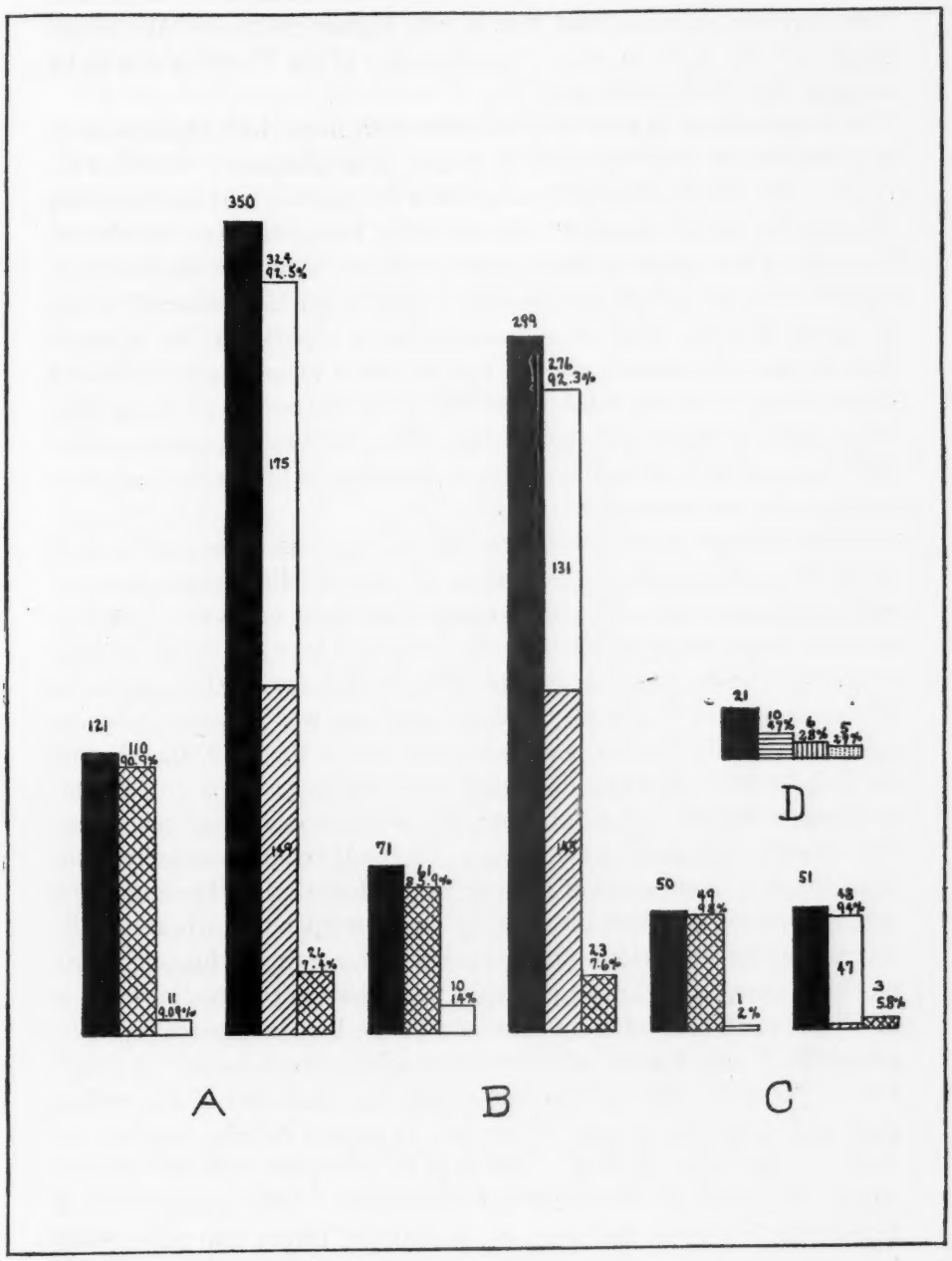
121
110
90.9%
11
9.09%
350
324
92.5%
175
149
24
7.4%
71
61
85.9%
10
14%
299
276
92.3%
131
143
23
7.6%
50
49
98%
1
2%
51
48
94%
47
3
5.8%
21
10
47%
6
28%
5
23%
D
A
B
C

CHART 1

reaction, slightly more than 50 per cent reacted to the 1:10,000 dilution (the Mantoux dilution) and not to the higher dilutions. We would emphasize this point in view of the advocacy of the Mantoux test as an accurate diagnostic procedure.

It is interesting to note that one nontuberculous child, eight years of age, reacted to 1:10,000 and not to the higher dilutions. We have recently seen several other children between the ages of eight and ten years who gave a similar response. On the other hand, we have not yet encountered a case under the age of eight years which failed to show definite reactivity to all dilutions in the series, when a reaction occurred to the 1:10,000 dilution. This would seem to be of importance, for it would indicate that the quantitative tuberculin test is unnecessary in children under the age of about eight, a reaction to the Mantoux test being sufficient from a diagnostic standpoint. This relieves the diagnostician from the necessity of making multiple injections in young children, who are apt to be unmanageable.

Included in this series are 141 cases tested with both human and bovine tuberculin. Twenty-three were cases of proved tuberculosis, and 118 were nontuberculous. Of the 23 tuberculous cases so tested, 4, or 17.3 per cent, would have been missed, had only one type of tuberculin been used. Of these 4 cases, 3 were positive to all human dilutions and to bovine in only the 1:10,000 dilution, while one was positive to bovine tuberculin in all dilutions, and to human in only the 1:10,000 dilution. In their series of 51 cases, Downing and Higgins reported 16 per cent reacting to the bovine type of tuberculin, which would have been missed had only the human type been used. Of the 23 tuberculous individuals thus tested, 21 were cases of bone or joint tuberculosis. In contrasting the intensity of reaction obtained in the corresponding wheals of the human and bovine series in the bone or joint cases, it was found that 10, or 47 per cent, reacted more intensely to the bovine tuberculin, while 6, or 28 per cent, reacted more intensely to the human tuberculin. The remaining 5 cases reacted with equal intensity to both series. A difference in intensity was recorded only when the diameters of the wheals produced varied by several millimetres, or when a definite reaction occurred to the high dilutions of one type of tuberculin, with no response to the corresponding dilutions of the other series. This appears to be of importance in view of the commonly entertained theory that tuberculous bone and joint cases are due largely to infection with the bovine type of tubercle bacilli. The finding in this very small group of cases would seem

to confirm the work of Griffith, who was able to culture bovine tubercle bacilli in about 20 per cent of the tuberculous bone and joint cases which he studied (19).

Of 26 individuals considered to be nontuberculous, who gave a positive reaction in all dilutions, 8 were specifically admitted for joint conditions. The others had been hospitalized for conditions other than tuberculosis, and consequently were not followed up in sufficient detail while in the hospital, to establish the presence or absence of some hidden active tuberculous lesion. We are by no means certain that a careful follow-up of these positively reacting cases would not establish the actual clinical presence of some tuberculous focus.

SUMMARY

A differential quantitative intracutaneous tuberculin test has been described, using potent human and bovine tuberculin in parallel series. The dilutions used are so chosen that the basic dilution is of a potency comparable to that of the Mantoux test, and the series extends to dilutions sufficiently weak to exclude all but the truly hypersensitive tuberculin reactors. These dilutions, with tuberculin of a potency usually found in commercial samples, range from 1:10,000 to 1:10,000,000. Inclusion of both human and bovine tuberculin diminishes the possibility of missing occasional cases, which might be overlooked when only one type of tuberculin is used.

A total of 471 cases is reported, comprising children and adults, tuberculous and nontuberculous. Of 121 tuberculous cases, 90.9 per cent reacted positively to the diagnostic dilutions, and 9 per cent gave a negative reaction. Of 350 nontuberculous cases, 92.5 per cent gave a diagnostically significant negative reaction, and 7.4 per cent reacted to the diagnostic dilutions. Of 23 tuberculous cases tested with both human and bovine tuberculin, 4 (17.3 per cent) would have been missed had only one type of tuberculin been used.

CONCLUSIONS

The differential quantitative intracutaneous tuberculin test should be considered as a valuable confirmatory diagnostic procedure, when used in conjunction with other available data. Its accuracy is comparable to that of the commonly accepted immunological and serological diagnostic procedures. The possibility of missing occasional cases is diminished by

the use of both human and bovine tuberculin. The method is safe, for the actual quantity of tuberculin used is infinitesimal, and it is administered in such a manner that absorption is necessarily slow, thus avoiding any focal or general reaction.

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THE INCIDENCE OF TUBERCULOUS INFECTION IN CHILDREN AS BASED ON 3,500 INTRACUTANEOUS TUBERCULIN TESTS[1,2]

LLOYD B. DICKEY AND ROLAND P. SEITZ

This study was begun in 1925 with the support of the San Francisco Tuberculosis Association. A preliminary report detailing an analysis of 500 of these cases has been published (1).

With readings on 3,500 children now recorded we believe a true incidence of tuberculous infection within the age-group for this community has been established. A knowledge of this incidence affords a reliable guide to the amount of infection and is imperative to the formation of proper control and remedial effort. Many studies have appeared in the literature for various communities, but most of them have been with the less accurate cutaneous test. Pirquet's series (2) and those of others (3) (4) (5) (6) from Europe were done with this method, as well as Veeder and Johnston's (7) from St. Louis, Sill's (8) from New York, and those of Ferguson (9), Slater (10), and Vories (11) from rural communities in America.

In our series the children were unselected and tested regardless of the presenting complaint as they registered in the Children's Clinic of the Stanford University Medical School. The dispensary is a part-pay clinic which admits some indigent patients and none of the well-to-do. The large majority of those attending are members of families where the income is adequate for maintenance, but not for medical care.

Hamburger (12) questions the reliability of using dispensary children in determining the incidence of tuberculous infection, claiming that it will be higher than among the population at large. This might be especially true for the European clinics, which are mostly attended by the indigent, or for other clinics a decade ago. In clinics of the present day in America there are coming, in always increasing numbers, children

[1] From the Department of Pediatrics, Stanford University Medical School, San Francisco, California.

[2] Read before the Second International Pediatric Congress, Stockholm, Sweden, August 18, 1930.

with no complaints whatever, who attend for advice as to feeding and diet, habits, for prophylactic measures against certain communicable diseases, and for minor complaints. The use of the dispensary at the same time allows an inclusion of the ill, thus permitting the determination of an approximate mean of tuberculous infection of children, including both sick and well.

In our series the dosage used was 0.1 cc. of a 1:1000 dilution of Koch's Old Tuberculin in physiological saline solution, thus making the standard 0.1 mgm. of tuberculin. All tests were done intracutaneously, according

TABLE 1

The results of intracutaneous tuberculin tests, according to age and sex-groups

AGE	MALE			FEMALE			TOTAL		
	Number done	Number positive	Per cent positive	Number done	Number positive	Per cent positive	Number done	Number positive	Per cent positive
1	100	6	6.0	79	4	5.1	179	10	5.6
2	114	14	12.3	99	15	15.2	213	29	13.6
3	132	24	18.2	111	17	15.3	243	41	16.9
4	173	39	22.5	155	26	16.8	328	65	19.8
5	173	33	19.1	138	31	22.5	311	64	20.6
6	181	28	15.5	159	28	17.6	340	56	16.5
7	212	29	13.7	167	32	19.2	379	61	16.1
8	178	41	23.0	144	44	30.6	322	85	26.4
9	133	33	24.8	127	39	30.7	260	72	27.7
10	121	30	24.8	127	35	27.6	248	65	26.2
11	116	46	39.7	105	38	36.2	221	84	38.0
12	107	43	40.2	72	27	37.5	179	70	39.1
13	93	40	43.0	68	28	41.2	161	68	42.2
14	66	29	43.9	50	25	50.0	116	54	46.6
Totals...	1,899	435	22.9	1,601	389	24.3	3,500	824	23.5

to the method of Mantoux (13), on the flexor surface of the forearm. During the first part of the study a distal control of normal saline solution was used. None of these controls reacted and later the practice was discontinued. The experience of Smith (14) has been that a blank broth control is equally valueless. An erythema, 5 mm. in diameter at 48 hours, was taken as the minimum positive reaction, the standard set by Pirquet in his original communications (15) (16).

Of the 3,500 children tested 824, or 23.5 per cent, reacted positively. The results, divided into age- and sex-groups, are shown in table 1. When these findings are graphically charted (chart 1) there is demon-

strated a slightly irregular, but steady ascent of the curve proportionate to age for both sexes. This is not regularly seen with the results of the Pirquet test. The percentage of 46.6 at age 14 is, we think, particularly significant because it represents the incidence of tuberculous infection at the approximate transition from childhood to adult life.

While there is a general ascent of the curves for both sexes, they are not parallel, and cross at several places. In the studies of Harrington and Myers (17) the curve for boys was generally higher. Hetherington

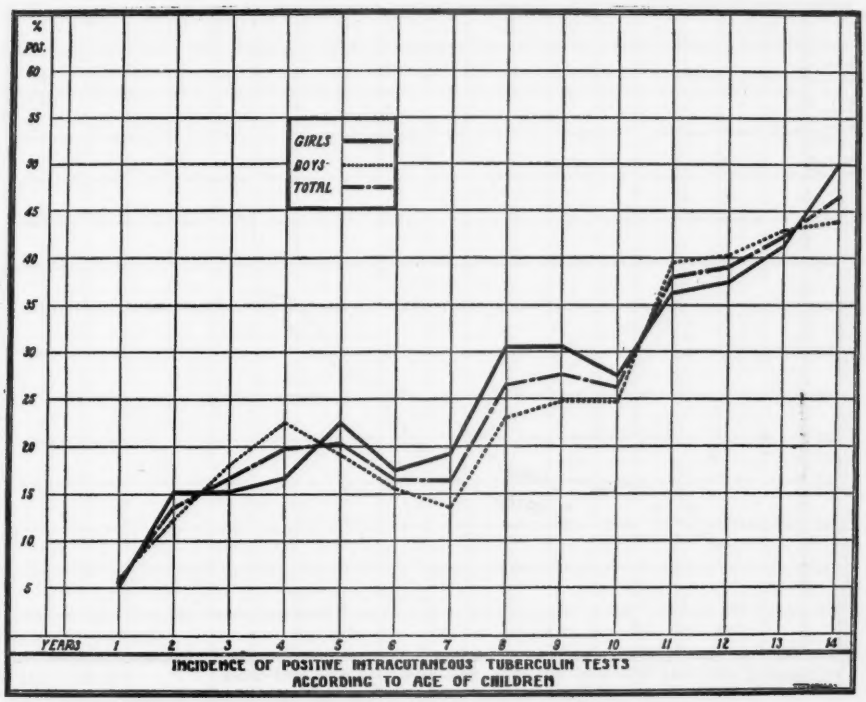

CHART 1. The results from table 1, graphically charted

and others (18), on the other hand, found a higher incidence among the girls in their investigation and say, "Infection in childhood is probably acquired in very large part by contact with open tuberculosis in some member of the family. It is probable that girls still spend a larger part of their time in the house than boys and are thus exposed to more intimate contact with members of their family who suffer with tuberculosis." However we think it is logical to presume that the chances of becoming infected are at least equal among boys because of their more

numerous casual contacts and this would counteract the more intimate association of girls with fewer individuals.

When the figures in our series are arranged into larger age-groups by the conventional method of eliminating the chance error of smaller numbers of figures, the curves become more smooth. In chart 2 it is seen that there is a moderate "slowing up" of the incidence at ages five and six for both sexes. At this time the incidence for boys, previously higher, sinks below that of the girls, where it remains until gaining the

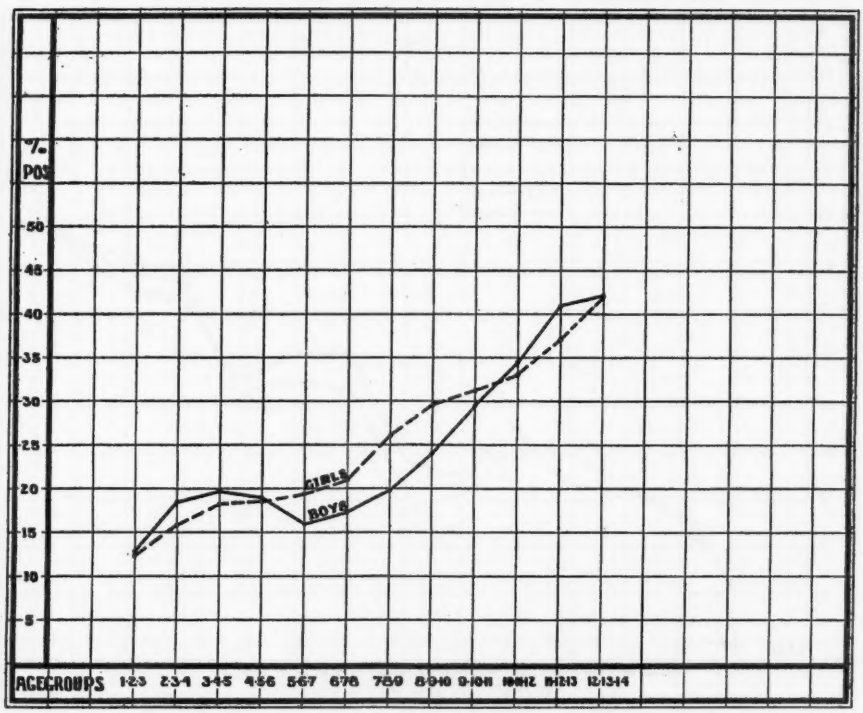

CHART 2. The results from table 1, for each sex, when larger age-groups are used to smooth out the curves.

ascent again in the last few years of childhood. When the totals for both sexes are considered together, the ascent is almost a straight line after the depression in the curve at ages of five and six (chart 3).

Hamburger (12) has repeatedly called attention to the inaccuracy of the Pirquet test and says in this respect, "I have called attention again and again to this unreliability of the Pirquet reaction and particularly in my monograph on tuberculosis in childhood, but I regret to say, with-

out much success." The recently published studies of Smith (14) and of Taylor (19) prove again what Hamburger and others have stated. Because this is so, studies with the Pirquet test in the past and even now appearing must be discarded as inaccurate and erroneously low.

In table 2 we have collected the results of intracutaneous tests done in the United States and Canada and we have also added some of the more representative figures from other places. The data are tabulated for ages approximating adolescence and show marked variation.

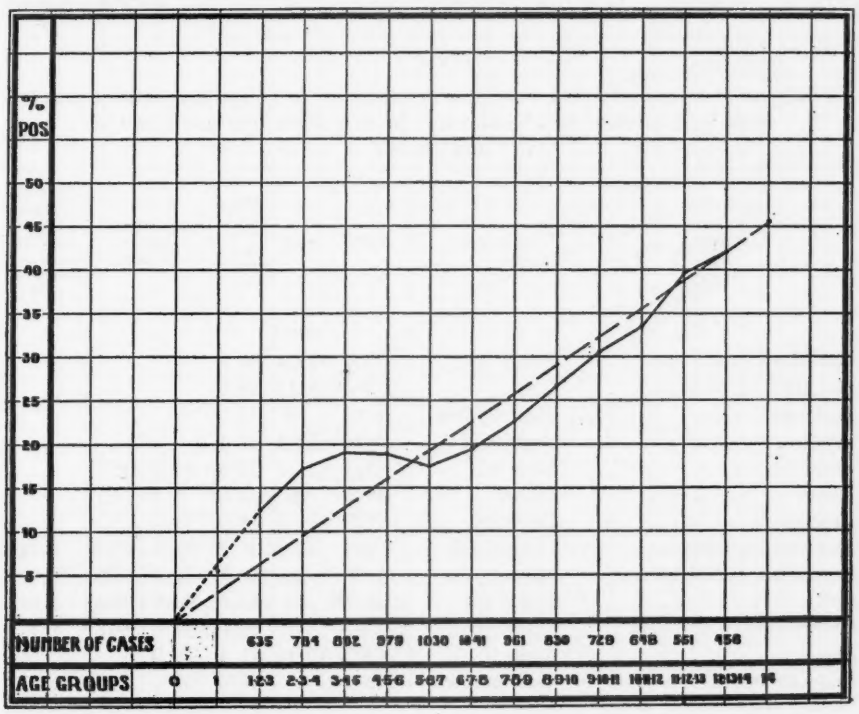

CHART 3. Using data from table 1, for both sexes, by method the same as for chart 2, curve of incidence and base-line.

Several possible explanations for differences of the results obtained by different students for variability may be given. Hamburger and Monti (20) examined only children in a public hospital convalescing from scarlet fever and diphtheria. Except that these children were presumably of a poorer class this woud be a fairly representative series. Krogsgaard's (21) series was very small in the age-group here considered. The percentage quoted for Opie and McPhedran (22) is only for children in

whom no history of contact was obtained. Barchetti (23) and Sander (24) reported on clinic children among whom were included large numbers of contacts with tuberculosis. Harrington and Myers and Hetherington and others report only on school children who were presumably well. Similarly both Elliott (25) and Baker (26) examined children of this same group in rural communities and Garrahan (27) reports on institutional children. Taylor, while she examined hospital children, excluded clinical cases of tuberculosis and her patients were essentially rural in residence. It is not unreasonable to conclude that surveys made

TABLE 2

The incidence of tuberculous infection at ages near adolescence for various communities, as determined by intracutaneous tuberculin tests (those of Hamburger and Monti by "Stich" method)

AUTHOR	LOCATION	YEARS	AGE	PER CENT POSITIVE REACTION	MORTALITY RATES PER 100,000	CASES OF TUBERCULOSIS PER 1,000 INHABITANTS IN 1928
			years			
Hamburger and Monti	Vienna	1909	12–14	94.3		
Barchetti	Graz	1917–21	11–14	58.0		
Garrahan	Buenos Aires	1918	15	75.0		
Sander	Dortmund	1921	13–14	48.2		
Baker	Alberta	1924	13–17	22.8	52.0 (1921)	
Elliott	Ontario	1925	14	46.0	71.0 (1921)	
Krogsgaard	Denmark	1925	10–15	48.0		
Opie and McPhedran	Philadelphia	1926	10–14	46.3	95.9 (1926)	1.42
Harrington and Myers	Minneapolis	1926	15	50.7	52.6 (1926)	2.11
Smith	New York	1921–28	13	43.0	93.9 (1926)	1.94
Hetherington and others	Philadelphia	1926–29	15	81.0	84.0 (1928)	1.42
Taylor	Iowa	1930	13–16	31.4	35.0	0.64
Present authors	San Francisco	1925–28	14	46.6	107.6 (1926)	1.95

to-day are not wholly comparable with those of a decade ago even though they be performed under identical conditions and in the same community. Mortality rates from tuberculosis are everywhere reported lower and it is possible that this might be reflected in some communities in lowered incidence as well. It would be interesting and important to make tuberculin studies at fairly frequent intervals in the same areas.

It is striking that the percentage of 81 obtained by Hetherington and others in school children should so closely approach that of Hamburger and Monti in Vienna which is 94.3 per cent. The latter authors ob-

tained this rate in a slightly younger, and a hospital group. It is noteworthy that two widely differing rates quoted for the same city in our table were in part done by the same investigators. The obvious explanation is that the groups studied are not comparable. Again, Smith's average on patients we would expect to show a very high incidence is in contrast quite low.

Chart 4 emphasizes the correlation between age and incidence in

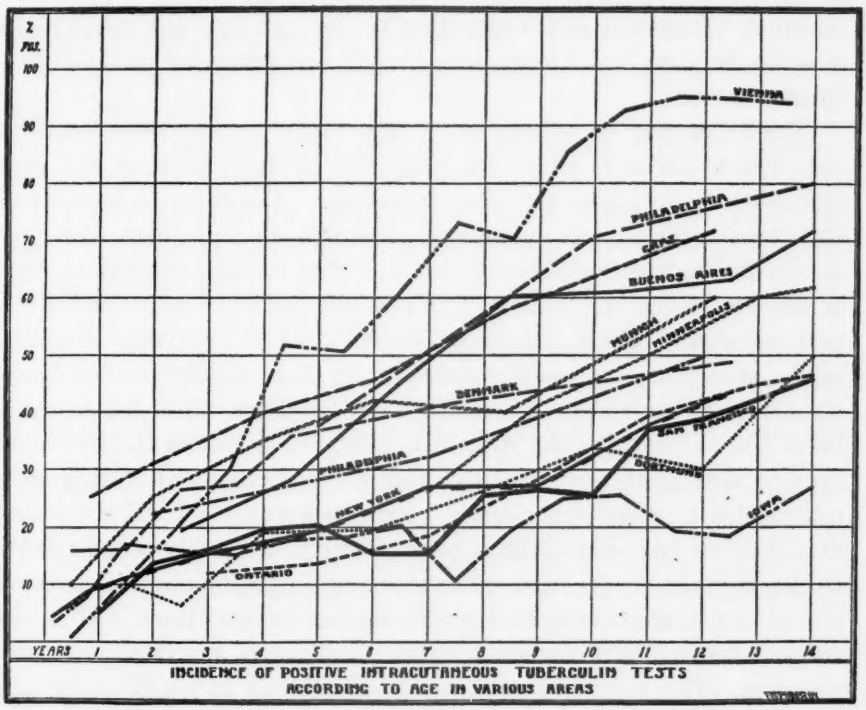

CHART 4. Curves showing the incidence of infection from various localities. From figure 11 of Smith's report, with additions.

most of the same studies we have previously tabulated. This chart is taken from Smith (14) with several new additions.

In general it may be said the number of individuals in any community infected with tuberculosis depends rather on the opportunities for becoming infected than on race, economic status or climate. Many studies have appeared which show these opportunities for infection in the different races, in diverse social strata and in varying climate.

There have appeared reports showing the amount of infection in

various races (African Negro (28), American Indian (29), Orientals (30) in California, in India (31), Chinese (32)), but the differences are not racial *per se*. The amount of infection has rather closely paralleled in some instances the mortality of that race from tuberculosis and hence reflected again no more than the opportunity for infection.

It is again apparent that morbidity in Vienna, in the tenement districts of New York and in well-to-do rural communities are dependent only indirectly on economic status but directly on chances of exposure to infection. Barchetti called attention to the fact that the tuberculous infection in Graz and Vienna was directly proportionate to the tuberculosis mortality.

Climate cannot be considered a true factor in our considerations except in so far as it affects the migration of those diseased and thus increases or decreases sectional morbidity. Colorado, Arizona and California, with climate supposedly favorable for the tuberculous, are among the highest in morbidity and mortality in the Registration Area of the United States. Similarly an opposite influence accounts for the practical absence of tuberculosis in Central Africa and the Arctic Regions.

The incidence of tuberculous infection in clinic children in San Francisco is much lower than that of the European cities. It is considerably lower than in most of the American cities, where school-children were used to determine the incidence, and where methods of testing were comparable to those in our series. Reference to table 2 will show that in only a few instances is the amount of infection directly proportionate to the mortality rates from tuberculosis or to the number of cases reported, the most striking incidence being that of rural Iowa. All of the cities, however, have higher rates of infection, of mortality, of cases reported. The mortality rate from tuberculosis in cities cannot be used to judge the amount of infection among children for several reasons, the main one being that cases of open tuberculosis among adults are dealt with differently in various communities. In cities, such as Minneapolis, where a large number of patients die in sanatoria outside of the cities, the mortality rates will not give a real clue as to the chances of infection possible for children. Inversely the high mortality rates in California cities, where patients may have moved from their homes after the disease has been recognized and away from children, are no true means of judging the chances of California children for infection.

The most plausible explanation of lessened incidence of infection among children anywhere is the early recognition of open cases as sources

of infection where these are many, and then early removal from an environment where they may serve as contacts to susceptible children.

CONCLUSIONS

1. The results of 3,500 intracutaneous tuberculin tests are reported.
2. The incidence of tuberculous infection, as shown by such tests, increases with age.
3. The incidence for the vicinity of San Francisco is 46.6 per cent at 14 years, about the beginning of adult life.
4. This rate is compared with those obtained by similar methods in other communities.
5. The Pirquet tuberculin test should not be employed in studies of this kind, since it gives erroneously low figures.
6. Frequent surveys of representative cross-sections of the child population in all communities would be valuable to show the changing conditions of exposure.

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THE CHEMICAL COMPOSITION OF THE ACTIVE PRINCIPLE OF TUBERCULIN

XIV. ANALYSIS OF THE COLLOIDAL COMPONENTS OF TUBERCULIN WITH SPECIAL REFERENCE TO THE RELATION OF PROTEIN AND CARBOHYDRATE[1]

FLORENCE B. SEIBERT AND BETTY MUNDAY[2]

Much evidence (1) has been presented from this laboratory in recent years to show that the substance in tuberculin responsible for producing the skin reaction in tuberculous animals is the protein. There has been no reason to change this idea, but evidence has accumulated to indicate that the specific activity must be associated with more than one molecular entity. For example, in a series of tuberculin products obtained by coagulating at different temperatures, by fractionally precipitating by different concentrations of salts, or by mildly hydrolyzing the tuberculin, whole series of active fractions are obtained. It is clear that all of these fractions cannot have identically the same chemical structure. By these procedures, whole series of protein bodies, varying in the numbers of amino acids in the various complexes, are obtained; in other words, a series including protein, proteoses and peptones.

It is not inconceivable, then, that the specific tuberculin activity may be associated with a certain portion of the whole protein molecule, and that it may be possible to split off parts and even large parts, without injuring the essential grouping necessary to elicit the specific reaction in the tuberculous animal. With such an hypothesis in mind, the following research was undertaken in order to determine how small a molecule is able to produce the skin reaction.

Assuming that there is present in tuberculin a whole series of protein bodies of varying sizes, the aim would therefore be to separate them from each other for isolated study.

The method of ultrafiltration through graded ultrafilters, previously used by one of the authors (2), was chosen as a means of separating the

[1] Aided by a grant from the National Tuberculosis Association.

[2] The Otho S. A. Sprague Memorial Institute and the Department of Pathology, the University of Chicago.

different-sized particles, for several reasons. In the first place, Bechhold's (3) gradation of membranes, according to the molecular size of particles which passed through them, is available as a basis for comparison of the results obtained. The part that the charge of the particle is able to play in any such method, as pointed out by Kramer (4), of course, cannot be overlooked. Moreover, the desirability of leaving the various particles with their natural configuration and associations unchanged favored the use of the ultrafiltration mechanical means of separation.

Such a separation is theoretically ideal, but the analyses have shown that in the case of tuberculin a clear-cut separation cannot be made in this way, because of the presence of a polysaccharide which also is a large colloidal molecule and which, because of its acidic nature, combines with various protein fractions. Only an estimate, therefore, of the molecular size can be made, by these studies, but even this will afford valuable information, and although the complete chemical identification of the smallest biologically active molecule has not yet been made it seemed advisable to report at this time the data so far obtained. Work is in progress.

Every effort was made to follow by analyses, not only the protein bodies, but also the carbohydrate, in order to determine their relative size, affinity for each other, their distribution, and, of course, their relation to the biological potency of the fractions.

The cause of the toxicity of tuberculin can well be considered in this study. By this toxicity is meant the killing power not only in sensitive tuberculous but also in normal uninfected animals. For example, two to three milligrams of a human-type tubercle-bacillus tuberculin preparation will kill in forty-eight hours a tuberculous guinea pig of 400–500 gm. weight, whereas 100–150 mgm. of the same preparation is required to kill a normal guinea pig of similar size, the two animals dying with practically the same symptoms. To both animals, the material is toxic in comparison with a timothy-bacillus protein preparation, of which 100 mgm. is required to kill a tuberculous guinea pig and 1000 mgm. is needed to make a normal guinea pig ill.

The question as to whether this toxicity of the tuberculin is due to the same cause as the skin reaction is important, particularly when methods of standardization are being considered. Dorset (5) has indicated quite definitely his view that they are not identical. The carbohydrate has been considered by White (6) to be a toxic element. It is well known that proteoses cause shock reactions in animals, and the symptoms manifested bear close resemblance to tuberculin deaths. Since protein cleav-

age products are without question present in tuberculin, and especially in Koch's Old Tuberculin (O.T.), they might well be suspected to be a cause of toxicity, and the data obtained lend support to this conception.

The procedures for differentiating between various cleavage stages of a protein are uncertain, and one must be satisfied, at present, with rather gross methods for distinguishing between them. Some attempt has been made in this paper to follow their presence in order to determine the rôle they play in the toxic symptoms displayed by the animal injected with tuberculin. The presence of such derivatives was ensured in one experiment by performing a mild hydrolysis, such as occurs in preparing O.T.

EXPERIMENTAL

The tuberculin used in these two experiments was made by Miss Nelle Morley, by growing the human-type tubercle bacillus (strain H37) for eight weeks upon the Long (7) synthetic medium.

In experiment 1 twelve litres of such tuberculin obtained by filtering off the bacilli through the Berkefeld were concentrated by ultrafiltration to 180 cc. through 12 per cent gun-cotton glacial-acetic-acid membranes (2), making a 66.6 times concentration. This was known as BBc tuberculin. It was preserved with 0.5 per cent phenol. One hundred and fifty cubic centimetres of BBc, corresponding to 10 litres of original tuberculin from an eight week's growth, were actually used in the procedure outlined under the heading experiments 1 and 2.

In experiment 2 the equivalent of 9 litres of tuberculin of a similar 8 weeks' culture of H37 strain human-type tubercle bacillus was this time heated with the bacilli for five hours on the steam bath, and then filtered free of bacilli through the Berkefeld, leaving a volume of 8800 cc. This then was concentrated further on the steam bath to 800 cc. and filtered free of any sediment through paper. It was called OT_3 and had been concentrated 11 times. Three hundred cubic centimetres of OT_3 were actually used in the procedure outlined under experiments 1 and 2.

Experiments 1 and 2: Simultaneously the two tuberculins just described were treated as follows: Each (150 cc. BBc. and 300 cc. OT_3) was filtered through membranes made from an 8 per cent[3] gun-cotton solution. They were further washed with 0.5 per cent phenol solution until the filtrates gave a negative biuret, Cl and Fe test, and then they were

[3] These solutions were not true per cent solutions, but, because of convenience in handling, an 8, 10, 12, 13 per cent membrane was really made by dissolving 8, 10, 12 and 13 gm. respectively of soluble gun-cotton in 100 cc. glacial acetic acid.

taken to dryness *in vacuo* over $CaCl_2$. These fractions are known as BBc (1) and OT_3 (1). In this way all the molecules were isolated which were large enough to be held back by an 8 per cent membrane, and they were washed free of all the smaller molecules. Only adsorbed or combined particles or particles of similar size remained behind in these fractions.

The entire filtrate, in each case, consisting of 4–5 litres, was then filtered through 10 per cent membranes and similarly washed until the filtrates gave negative tests for biuret, Cl and Fe, and then they were dried to powder form. In this way all the particles small enough to pass the 8 per cent membranes but large enough to be held back by the 10 per cent membranes were isolated. These were known as BBc (2) and OT_3 (2).

In a similar manner the filtrates from these filtrations were passed consecutively through 12 and 13 per cent membranes and the particles large enough to pass the 10 per cent membranes but small enough to be held back by the 12 per cent membranes were separated (BBc (3) and OT_3 (3)). Those small enough to pass the 12 per cent membranes but large enough to be held by the 13 per cent membranes were also isolated (BBc (4) and OT_3 (4)). In the case of the BBc these last two fractions were so small that they were combined and even then only equalled 0.5 per cent of the entire solid content (BBc (3)). (See table 3.)

The final filtrates, equalling about 6 litres each, also were saved and concentrated (to 100 cc. in the case of BBc filtrate, and 190 cc. in the case of OT_3) *in vacuo* at 40–50 degrees and saved for analyses. The solid content of these solutions, however, would mean nothing, since all medium constituents, salts, glycerol, etc., were present.

Column 1 in table 3 shows in percentage the amounts of solid material isolated in the different fractions, and that a much larger proportion of the OT_3 was in the form of smaller molecules, there being 16.5 per cent small enough to pass the 10 per cent membrane, whereas only 0.5 per cent of the BBc tuberculin fell in the same class.

Molecular size: At the same time, several substances of approximately known molecular weights were tested for their filterability through membranes made in exactly the same way. Several membranes were used in each experiment, so as to eliminate errors which might possibly be due to leakage. In table 1, plus indicates that the substance passed the membrane and was found in the filtrate. Molecular weights, estimated from Bechhold's (3) data, are listed. The proteose preparation was made from Witte's peptone by filtering off a trichloracetic-acid precipitate and

dialyzing the filtrate in parchment, and then drying the nondialyzable or proteose residue.

Therefore, since only traces of active material of tuberculin pass through a 12 per cent membrane, as will be shown later, it can be said that the smallest molecule giving a marked tuberculin skin reaction and containing lethal powers and antigenic properties is somewhere near the size or smaller than the litmus molecule. The possibility of error in drawing such analogy is recognized. (See discussion concerning the relationship between protein and carbohydrate later on.) But the fact is clear, however, that a molecule as small as or smaller than the litmus molecule, which has a molecular weight around 1000 to 2400, is able to produce the tuberculin reactions. Krueger and Ritter (8) have recently shown that the diameter of the litmus molecule is 2 $\mu\mu$.

TABLE 1

SOLUTIONS	ESTIMATED APPROXIMATE MOLECULAR WEIGHT	FILTRATES FROM MEMBRANES		
		8 per cent	10 per cent	12 per cent
Inulin (dextrin) 2 per cent	965	+	+	+
Proteose from Witte's peptone	?	+	+	+
Litmus (0.33 per cent)	Between 965 and 2400	+	+	− (trace)
Crystallized egg albumin	34,000	−	−	−

ANALYSES

All fractions were then analyzed for total N, amino N and N precipitable by trichloracetic acid, and for carbohydrate content as determined directly and after hydrolysis. The results are recorded on the basis of dry weight, the samples containing from 6–8 per cent moisture.

Methods

1: Total *nitrogen* was determined on 10–20 mgm. samples by means of the microkjeldahl methods, using $CuSO_4$ and Na_2SO_4 in the digestion mixture and terminating in a titration with 0.01 N/NaOH, using methyl-red as indicator. The error in this method was less than 1 per cent.

2: Amino nitrogen was determined by the micro Van Slyke method.

3: The nitrogen precipitable by trichloracetic acid was determined by the following method: To 1–2 cc. of solution containing 10–20 mgm.

of the sample was added 8 cc. *fresh* 10 per cent trichloracetic acid and the whole made up to 10 cc. This then was poured into a centrifuge tube and allowed to settle over night, centrifugated until clear, and the nitrogen in 8 cc. of the clear solution determined by the above method. The amount of precipitable nitrogen was then found by subtraction from the total nitrogen.

4: The *carbohydrate* was determined by the Shaffer-Hartman cuprous titration method, as follows: To 5 cc. of the unknown solution was added 5 cc. of the recently modified reagent (25 gm. anhydrous Na_2CO_3, 20 gm. $NaHCO_3$, 25 gm. Rochelle salt, 7.5 gm. $CuSO_4$ and 100 cc. of 0.1 N/KIO_3 solution per litre). This was boiled exactly 10 minutes in a water bath, cooled, and to it added 1 cc. 2.5 per cent KI, 5 cc. N/H_3SO_4 and 1 cc. starch solution. This then was titrated with 0.005 N/$Na_2S_2O_3$. The number of cubic centimetres of $Na_2S_2O_3$ divided by 8.5 = milligrams of carbohydrate, calculated as glucose, in the solution.

TABLE 2

Per cent of carbohydrate

	10 MINUTES	1 HOUR	2 HOURS	3 HOURS	5 HOURS	7 HOURS	10 HOURS
	per cent	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*
(1)	7.9	12.3	13.1	14.3	16.5	16.8	14.8
(2)	5.7	9.8		11.2	13.1	15.2	13.4

Since only a very small amount of the tuberculin carbohydrate will reduce, unless previously hydrolyzed (9), the amount of reducing substance after hydrolysis was also recorded. In each case 15.625-cc. portions of the solution were refluxed with 0.5 cc. concentrated H_2SO_4 in a water-bath for seven hours, neutralized with NaOH, and made up to 25 cc. The seven-hour period for hydrolysis was chosen after the following two experiments on two different tuberculin-protein preparations indicated that at that time the hydrolysis was complete.

In table 3 are given the results of analyses by these methods of the fractions separated during ultrafiltration. All of the fractions were completely or almost completely water-soluble, except the BBc (1) fraction. This required a small amount of alkali to effect solution and then, if immediately neutralized, the solution became somewhat opalescent. On standing for days a precipitate settled out. The other solutions remained clear for a long time.

It is evident that the nitrogen content of the fractions decreases with the decreasing size of the molecule. And, furthermore, the nitrogen content of the larger molecules, as would be expected, is in a form which is precipitable to a larger extent by trichloracetic acid. Conversely the carbohydrate content increases with decreasing size of molecule. It is noteworthy that all fractions contain considerable reducing substances; and those fractions falling in size between the pore size of an 8 and a 10 per cent membrane contain almost as much reducing substance as the pure carbohydrate itself.

TABLE 3

Chemical analyses

SUBSTANCE	PER CENT OF WHOLE BY WEIGHT	PER CENT NITROGEN			PER CENT REDUCING SUBSTANCES (AS GLUCOSE)		
		Total	Per cent of total precipitated by trichloracetic acid	Amino	Unhydrolyzed	Hydrolyzed	Total
Exp. 1—BBc							
(1) held by 8% membrane	73.4	8.60	55.81	0.30	0.33	22.93	23.26
(2) held between 8–10% membrane	26.0	3.80	7.89	0.26	0.77	42.23	43.00
(3) held between 10–13% membrane	0.5	6.25*					
Exp. 2—OT_3							
(1) held by 8% membrane	30.2	13.67	58.15	0.93	1.07	10.85	11.92
(2) held between 8–10% membrane	53.1	6.78	28.76	0.55	1.34	33.72	35.06
(3) held between 10–12% membrane	14.1	5.27	0.00	0.38	3.36	25.70	29.06
(4) held between 12–13% membrane	2.5	3.69*					
Ammonium-sulphate precipitates							
M9-$\frac{1}{3}$ saturated fraction	58.0	16.11	86.03	1.08	0.00	2.77	2.77
M11-complete saturated fraction	20.0	11.96	71.15	0.26	0.94	21.60	22.54
M12-complete saturated (proteose)	14.3	12.30	15.36	0.86	1.02	22.44	23.46
M11P-complete saturated (purified)		14.80	60.81	0.70	0.00	8.18	8.18
M5-crystalline insoluble	2.8	16.86			0.00	0.93	0.93
M7-crystalline soluble	3.9	8.83			0.00	35.18	35.18
Acetic-acid precipitate		16.86			0.18	2.53	2.71
Trichloracetic-acid precipitate		14.98			0.38	2.36	2.74
Crystallized ovalbumin		14.73			0.00	0.12	0.12
Polysaccharide of tubercle bacillus		2.01			4.20	49.60	53.88

* Determined by Pregl's micromethod.

Biological Activity of Fractions: On each fraction, three types of biological tests were made.

1: The amount of skin reaction given by 0.1 mgm. when injected intracutaneously was noted in 400–500 gm. tuberculous guinea pigs. The animals had been inoculated subcutaneously with 0.1 mgm. H37 strain human-type tubercle bacillus five weeks previously. In experiment 1 the three fractions were injected simultaneously into each guinea pig, and in experiment 2 the four fractions into each guinea pig. Consequently, the skin tests, as recorded, are truly comparable, and a comparison between the potencies of the different fractions is not masked by varying sensitiveness of individual animals: 5–6+ indicates a maximum skin reaction with an area of necrosis from 0.5–2.0 cm., surrounded by a blanched area, and this in turn by a considerable and varying amount of inflammation; marked induration usually accompanies this type of reaction: 5+ indicates a slightly less marked reaction; 4+ only a small amount or no necrosis with marked induration; 3+ no necrosis and some induration; 2+ and 1+ very slight reactions.

2: The m.l.d. by intraperitoneal route for each fraction was determined in 400–500 gm. tuberculous guinea pigs which had been inoculated subcutaneously in the groin with 0.1 mgm. H37 tubercle bacilli five weeks previously.

3: The precipitin titre was determined, using each fraction as the antigen, by the method discussed in a previous communication (10). The serum was obtained from normal rabbits which had been injected five times intravenously with 10 mgm. of the whole protein (protein-carbohydrate complex) from the human-type tubercle bacillus and then bled after a three-week interval. Such serum (0.1 cc.) was placed in precipitin tubes and over it was layered 0.1 cc. of the antigen in varying dilutions. The titre, therefore, is the final dilution of antigen which gives a perceptible ring after two hours' incubation or a precipitate after standing over night. The serum from three rabbits was used in each case, but the first one had the highest titre.

Table 4 shows the corresponding biological reactions produced by the different fractions.

Discussion of Results: From table 4 it is apparent that, by and large, the active fractions are of such a size as to be held back by a 10 per cent membrane, and all smaller molecules contain none or only traces of reactive material, as determined by means of the skin, m.l.d. and precipitin tests.

Comparing table 3 and table 4 it would seem that the protein content of a preparation had much more to do with its biological properties than

TABLE 4

Biological activity of fractions

SUBSTANCE	MEMBRANE WHICH HELD IT BACK (PER CENT GUN-COTTON)	M.L.D.	SKIN TESTS WITH		PRECIPITIN TITRES	
			0.1 mgm.	0.01 mgm.	Ring	Precipitate
	per cent	*mgm.*				
BBc-1	–8	3	5+, 5+, 4+	5+, 5+, 4+	1: 40,000f	1: 40,000f
2	between 8–10	3	5–6+, 5+, 4+	5+, 4+, 2+	1: 10,000f	1: 10,000
3	between 10–13		3+, 1–2+, 1+	2+, 2+, –	1: 200	1: 2,000f
OT_3-1	–8	2.5	5+, 5+, 4–5+, 4–5+	5+, 3+, 3+	1: 1,000f	1: 200f
2	between 8–10	2	5–6+, 5+, 5+, 4–5+	5–6+, 4+, 2+	1: 20,000f	1: 20,000f
3	between 10–12	10	3+, 2+, 1–2+, 1+	1+, 1+, –	neg.	neg.
4	between 12–13	11	2+, 1+, 1+, 1+	1+, 1+, –	neg.	neg.
Ammonium sulphate fractionation						
M9-½ saturation precipitate		5	5–6+, 5–6+, 5+, 5+, 5+	5+, 4–5+, 4+	1:200,000f	1:200,000
M5-crystalline insoluble precipitate			3+, 2–3, 2+, 1+	1+, –, –		
M7-crystalline soluble precipitate		12	5+, 5+, 4+, 4+, 3+	2+, 1+, 1+		
M11-complete saturation precipitate		4	4–5+, 4+, 3+, 5+, 4–5+	3+, 1+, 1+	1: 40,000	1:100,000f
M11 P-complete saturation precipitate (purified)		9	5+, 4–5+, 4+	4+, 2+, 1+		
M12-complete saturation precipitate (proteose)		12	4+, 4+, 3+, 3+, 3+	2+, 1+	1: 400f	1: 400f
Polysaccharide		>50	–, –		neg.	neg.

TABLE 5

Minimal lethal doses

SUBSTANCE	SOLID PER M.L.D.	NITROGEN PER M.L.D.	GLUCOSE PER M.L.D.
	mgm.	*mgm.*	*mgm.*
BBc-1	3	0.26	0.70
2	3	0.11	1.29
OT_3-1	2.5	0.34	0.30
2	2	0.14	0.70
3	10	0.53	2.91
M9-½ saturated	5	0.80	0.14
M11-complete saturated	4	0.48	0.90
M11-P-complete saturated (purified)	9	1.33	0.74
M12-complete saturated (proteose)	12	1.47	2.82

TABLE 6

SUBSTANCE	SOLID FOUND	NITROGEN FOUND	GLUCOSE FOUND
	gm	*gm.*	*gm.*
Exp. 1. From 150 cc. BBc			
(1)	4.39	0.38	1.02
(2)	1.55	0.06	0.67
(3)	0.03		
Sum	5.97	0.44	1.69
Filtrate			0.18
Exp. 2. From 600 cc. OT_3			
(1)	1.57	0.22	0.19
(2)	2.76	0.19	0.97
(3)	0.74	0.04	0.21
(4)	0.13	0.004	
Sum	5.20	0.45	1.37
Filtrate			4.76

TABLE 7

	GRAMS REDUCING SUBSTANCE (AS GLUCOSE)		
	Unhydrolyzed	Hydrolyzed	Total
From 150 cc. BBc			
Total held back by all membranes of the series	0.03	1.66	1.69
Total washed through membranes	0.03	0.15	0.18
From 600 cc. OT_3			
Total held back by all membranes of the series	0.08	1.30	1.38
Total filtered and washed through membranes	0.66	4.10	4.76

did the carbohydrate content, and, furthermore, that the form of the protein molecule is important. It is, of course, striking to note that a fraction, such as the BBc (2), containing only 3.8 per cent N and 43 per cent carbohydrate, is as potent as it is. But that these figures are probably not as significant as they would at first seem to be follows from an analysis of table 5, where the actual amounts of protein and carbohydrate contained in a killing dose are calculated.

It was surprising to find the total solid content of colloids of the two tuberculins so nearly equal (table 6) and it was more surprising to find the actual sum-total amounts of nitrogen and glucose so nearly the same. Such close correspondence, however, makes the task of comparison a simple matter. The distribution of the nitrogen and the glucose, on the other hand, in the individual fractions is quite different in the two series. In the case of the partially hydrolyzed tuberculin (OT_3) more protein molecules were small enough to pass the 8 per cent membrane and large enough to be held back by the 10 per cent membrane, whereas in the natural unheated tuberculin most of them were large enough to be retained by the 8 per cent membrane. That the smaller protein molecules were cleavage products of protein can be seen by examining the percentages of total nitrogen which were precipitable by trichloracetic acid (see table 3). Furthermore, in both experiments the $\frac{\textit{free amino N}}{\textit{total N}}$ ratio increases with decreasing size molecule. According to Wasteneys and Borsook (11) this is a measure of the degree of hydrolysis of the protein.

The determination of the carbohydrate in the final ultrafiltrates from the 13 per cent membrane gives valuable information as to the size of the polysaccharide itself and as to its distribution (table 7). In determining the reducing substances directly in these solutions, however, it was necessary to remove the phenol used as preservative, since it, of course, would interfere with the final iodometric titration. This was done by shaking out with ether and then removing the remaining ether *in vacuo*.

In the BBc series the determination of carbohydrate in the ultrafiltrate shows that relatively little can be removed by washing by ultrafiltration. The original BBc tuberculin had been concentrated by filtering 10 litres through a 12 per cent membrane and this first ultrafiltrate is not included in this series. Only 10 per cent of the carbohydrate can therefore be washed out by ultrafiltration, and the carbohydrates remaining with the

protein-carbohydrate complex are either large molecules in themselves or else are absorbed or chemically combined with the protein molecules and in this way prevented from passing the membrane pores.

That the carbohydrate which passes through even the densest (13 per cent) membrane is still in polysaccharide form and not necessarily a partially hydrolyzed molecule is clear from the fact that most of it required hydrolysis by the usual method (for seven hours) before it would reduce copper. (See table 7.)

In a corresponding experiment on OT_3 all of the reducing substances from the entire 6600 cc. original tuberculin were present. Of this, only about 28–29 per cent remained behind with the protein fractions during filtration and 71–72 per cent filtered through. This filter-passing carbohydrate also was largely in the form of polysaccharide, as shown in table 7.

The pertinent question, of course, is why some of the carbohydrate does not pass through the membrane. For this and other reasons, the following experiment was undertaken.

EXPERIMENTAL

Ammonium-Sulphate Fractionation: From about a litre of highly concentrated (by ultrafiltration through 12 per cent membranes) tuberculin[4] a fractionation by means of ammonium sulphate was made. The fraction precipitating at half-saturation was removed, redissolved in water (pH 6.0–6.4), filtered, reprecipitated by half-saturation, and this process repeated four times. Then the dissolved precipitate was dialyzed in a fish-bladder membrane until free of sulphate and dried *in vacuo*. This was designated M9.

From the filtrate of the half-saturated fraction, crystals were obtained by the method previously described (1c). Unfortunately the quantity obtained was so small that only one crystallization could be performed, and therefore this fraction was not as pure as desired. It was, however, immediately put into a dialyzing sac and freed of ammonium sulphate. During this dialysis, which began with a solution at a pH of 4.8, considerable precipitation occurred, and at the end of dialysis the soluble (M7) and insoluble (M8) fractions were saved separately.

After these crystalline fractions had been removed from the tuberculin, the filtrate was completely saturated with ammonium sulphate. This

[4] This tuberculin was supplied by the H. K. Mulford Co. and was made exactly as described for the BBc.

complete-saturation precipitate had much more golden-yellow color than the half-saturated fraction. It was redissolved in water at pH 6.0–6.4, filtered and reprecipitated, and this process was repeated four times. The final precipitate was dissolved and dialyzed in a fish-bladder membrane until free of sulphate and dried *in vacuo*. It was called M11.

To the filtrate from the complete saturated fraction was added more solid ammonium sulphate, and on standing an additional precipitate settled out as a dark brown sticky mass adhering to the sides and bottom of the flask. The ammonium-sulphate solution was decanted from this mass, which was then dissolved in water at a pH of 6.0–6.4, filtered and reprecipitated, and this process repeated four times. The final precipitate was dissolved and dialyzed in a fish-bladder membrane until free of sulphate and dried *in vacuo*. This was fraction M12. It is called the proteose fraction because of its physical property of stickiness.

One gram of the complete-saturation fraction M11 was then purified further by redissolving and reprecipitating four more times, exactly as had been done previously, except that all dissolvings and precipitations were carried on at pH 4.8, since this pH had previously (1c) been shown to be the point of optimum crystallization, where also it was finally possible to obtain a crystalline fraction that gave a negative Molisch test. This purification process caused the fraction to lose two-thirds of its weight. The purified product is known as M11P.

Table 3 gives the chemical data and table 4 the corresponding biological potencies of these fractions.

DISCUSSION OF RESULTS

The half-saturated fraction contains very little carbohydrate, only 2.77 per cent, which is about the same amount as is contained in acetic or trichloracetic-acid precipitates of tuberculin. The last two products, however, are much more insoluble in water and because of this are, therefore, more difficult to work with than the half-saturated fraction. The half-saturated fraction itself is slightly less soluble than the complete-saturated fractions, but only a very small amount of alkali is required to effect complete solution, and then upon immediate neutralization with HCl the solution remains clear or opalescent. It is a very potent preparation, as indicated by the fact that a maximum skin reaction is produced by even 0.01 mgm., as seen in table 4. It is, furthermore, an excellent antigen in the precipitin test, while the complete-saturation fraction is less so and the proteose fraction practically not at all.

The Constituent Responsible for the Skin Reaction and the Antigenic Effect: A careful study of the tables (3 and 4) discloses the fact that the content of polysaccharide of any fraction does not determine the amount of skin reaction produced or the antigenic properties here studied. The protein seems, without question, to be the determining factor. Those fractions having the highest nitrogen content and consisting of the largest molecules are invariably the most potent fractions in these respects.

An exception is found in fraction M5, which, although it contains very high nitrogen and practically no polysaccharide, is still a somewhat inactive preparation. Considering the very great potency (even 0.01 mgm. gives a 5+ skin reaction) of fraction M9, the analyses of which reveal its composition to be quite similar, it would seem as though the protein in M5 had been considerably denatured and for this reason was less potent. That this is probably true is also supported by its marked insolubility compared with other fractions obtained just before and just after it in the order of isolation.

That the polysaccharide is a very effective haptene in the precipitin reaction, when the animals have been immunized with the whole dead bacillary bodies, is evident from the work of Mueller (12), Dudley and Laidlaw (13) and Heidelberger (14). Why immunization with the protein-carbohydrate complex, as used in the experiments here recorded, yields such different results from immunization with whole bacteria is an interesting immunological problem.

The Constituent Responsible for the Toxic Effect in Animals: The potency of the fractions, when graded on the basis of the m.l.d. test, while somewhat paralleling the skin-reaction potency, is not quite so easily assigned to its cause. It is true, however, that those fractions which are most potent from the standpoint of skin reaction and also as antigens are also decidedly the most potent in their killing effect. (Notice particularly fractions BBc (1) and (2), OT_3 (1) and (2), and M9 and M11.)

A study of table 5 brings out the fact that the m.l.d. of the second fractions in each series of tuberculin preparations contains less nitrogen than the other fractions. The view is favored that the killing power of a fraction may depend more upon its content of the first cleavage products of the protein than upon its content of polysaccharide or even total nitrogen. If this degradation of the protein proceeds further, as demonstrated by the analyses of trichloracetic-acid precipitable nitrogen, the toxicity is considerably lowered and we have relatively nontoxic fractions, such as OT_3 (3) and M12. In other words, the group or groups essential for provoking this reaction are probably attacked at this degree of cleavage.

In the case of the ammonium-sulphate precipitates, relatively more protein is contained in a m.l.d. than of the ultrafiltered fractions (table 5). This is true even in the M9 fraction, which was notably potent in the skin and precipitin tests. This discrepancy is hard to explain, but there is the possibility of a lowering of the toxicity, due to salt-formation.

That the presence of the polysaccharide may enhance the toxicity must, of course, be considered. The following facts render this unlikely, however: that fractions like OT_3 (3), M12 and M7, contain large quantities of the polysaccharide and yet are relatively nontoxic; according to our own experiments, the almost pure polysaccharide itself has relatively little toxicity for the tuberculous animal; and finally of the M9 fraction, which contains only 2.7 per cent polysaccharide, 5 mgm. will kill a tuberculous guinea pig in 24 hours. Of three different pure polysaccharide fractions studied, 25, 30 and 50 mgm., given intraperitoneally, were not sufficient to kill very sensitive tuberculous guinea pigs. More experimentation, however, is required to establish this point conclusively.

The primary toxicity for the normal guinea pig of the whole ammonium-sulphate precipitates of the human tuberculin protein has been a prominent phenomenon in much previous work. In other words, at times it has not been possible to inject as much of the protein into the normal guinea pig as was desirable for the purpose of immunization, because of the toxic effect of the protein upon the animal. Marked emaciation and cachexia, simulating tuberculosis symptoms and yet without autopsy evidence of the disease, followed repeated injections of these protein fractions into normal guinea pigs. Moreover, 150 mgm. and occasionally 100 mgm., given intraperitoneally, would kill a normal guinea pig within 48 hours. Such preparations contained 12 per cent N, 75 per cent of which was precipitable by trichloracetic acid, and 15–16 per cent polysaccharide. This, compared with the 1000 mgm. of timothy-bacillus protein, made by the same method, which was required to kill a normal guinea pig, denoted a real primary toxicity of the human tuberculin protein for the normal animal. However, when the M9 fraction, which contained 16 per cent N, 86 per cent of which was precipitable by trichloracetic acid, and only 2.77 per cent carbohydrate (as glucose), was tested, it was found that even as much as 500 mgm., given intraperitoneally, did not suffice to kill a normal guinea pig. In other words the primary toxicity was very much lowered by the purification process.

The Chemical Relationship of Protein and Polysaccharide: The analytical data presented favor the view that the polysaccharide elements

which are strongly acidic are chemically combined with the protein cleavage products and possibly even with the whole protein. The evidence in favor of this view is as follows: Carbohydrate, in the form of polysaccharide alone, is capable of passing through even the finest (13 per cent) membrane, for it is found (table 7) in the final filtrates in a form which necessitates hydrolysis before reduction of copper will occur. In spite of the fact that a certain amount has been shown to pass through the membrane, a considerable portion remains behind with the protein molecules, and washing with water does not remove it.

Physicochemical studies are in progress in order to investigate the possibility of a colloidal absorption between the two molecules, for the polysaccharide can be removed from the protein by redissolving and reprecipitating at a pH of 4.8. In a previous study (1c) it was pointed out that after several recrystallizations, which occur at pH 4.8, the carbohydrate had been removed, for the final product gave a negative Molisch reaction. Quantitatively, this is actually shown here to be the case in fraction M5, which contains only 0.93 per cent polysaccharide (table 3). Even without crystallization the polysaccharide can be removed, as shown in fraction M11P (table 3), when, by simply redissolving and reprecipitating four times at pH 4.8, the carbohydrate content was reduced from 22.54 per cent to 8.18 per cent and the nitrogen content correspondingly raised.

It is unfortunate that the amount of acidity (pH 4.8) which is required to release the polysaccharide from the protein is at the same time apparently sufficient to denature the protein, not only from the standpoint of solubility but also of biological potency, as was evidently true in fraction M5.

On the other hand, it is possible to prepare a very potent protein fraction, practically completely water-soluble and therefore undenatured, and at the same time almost free of the polysaccharide. (Probably, with more dissolvings and precipitations, even the 2.7 per cent can be lowered.) Such is fraction M9, with practically no primary toxicity but with a tremendous specific toxicity for the tuberculous animal.

Molecular Size: Returning to a consideration of the size of the molecule responsible for producing the specific skin reaction, no more definite conclusion can be reached at this time on the basis of the ultrafiltration experiments outlined, than that it is certainly no larger and is possibly smaller than those molecules just held back by the 10 per cent membrane.

The protein or proteose part of the protein-carbohydrate complex would, of course, by itself be smaller than the combination. We must, therefore, reach the conclusion that as small a cleavage product of the tuberculin protein as what we have arbitrarily called the "proteose" fraction is sufficient to cause a skin reaction or act as antigen for immune sera.

The following hypothesis is therefore submitted, that some groups or portion of the protein molecule are responsible for the specific skin reaction and the antigenic effect, and, moreover, they are not affected during the first cleavage stages of the molecule. During this early disruption period, however, some other groups are exposed which possess toxic power even for the normal animal. Continued cleavage, however, breaks down or otherwise alters so much of the molecule that the specificity, antigenicity and toxicity are all lost. Denaturation, which may not be so much of a hydrolysis as a polymerization, also tends to inactivate these essential groups.

SUMMARY

1. The tuberculin action of tuberculin protein, as seen, for example, in the skin reaction in tuberculous animals, appears to be due to a specific portion of the protein molecule, which seems to be present in the first, but not the subsequent, cleavage products obtained during hydrolysis of the protein. The smallest protein molecule in tuberculin capable of giving the reaction has probably a comparatively low molecular weight, of 1000–2400 or less as indicated by passage through membranes.

2. Only the protein and possibly its first cleavage products produce the precipitin reaction in sera from animals immunized with the protein-carbohydrate complex (that is, the whole ammonium-sulphate precipitate of the human-type tubercle-bacillus tuberculin).

3. The lethal power of the tuberculin in tuberculous animals and in normal animals is probably associated with the very early cleavage products of the protein.

4. Polysaccharide is chemically associated chiefly with the early cleavage products of the tuberculin protein and cannot be removed by washing, but is released at a pH of 4.8. Nearly one fourth of the polysaccharide in tuberculin is so associated. The rest of the polysaccharide, not bound to the protein, passes even the finest filtre used in these experiments.

5. With this information it has been possible to prepare in quantity an extremely potent tuberculin protein in the form of a powder, which is

practically completely water-soluble and therefore undenatured, and which has a nitrogen content of 16 per cent and a polysaccharide content of 2.7 per cent or less. Only 0.01 mgm. is required to produce a maximum skin reaction in sensitive tuberculous guinea pigs, and 5 mgm. is sufficient to kill such a guinea pig in 24 hours. It gives a very high precipitin titre with sera from rabbits immunized with the protein-carbohydrate complex of tuberculin (that is, the whole ammonium-sulphate precipitate of the human-type tubercle-bacillus tuberculin). The primary toxicity for normal guinea pigs is extremely low,—somewhere in the neighborhood of that of timothy-bacillus protein.

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EXPERIMENTAL TUBERCULIN PNEUMONIA[1]

ALFRED LARSON AND ESMOND R. LONG

It is generally assumed that the acute exudative response in the alveoli of the lung in fulminating tuberculous pneumonia is a manifestation of hypersensitiveness, called forth on the implantation of a massive dose of tubercle bacilli and their products on lung tissue made allergic through the presence of a focus of tuberculosis. It is further generally believed, on the basis of studies on the tuberculin reaction, that this exudative reaction is basically a response to the protein of the bacillus, this being the specific substance responsible for the tuberculin reaction. But it is obvious that a considerable degree of nonspecific foreign-body reaction would also occur in addition to the specific element on the aspiration of the contents of a tuberculous cavity or ulcerated lymph node.

It is indeed reasonable to suppose that tuberculoprotein might incite an acute exudative process in the lung which, if severe enough, might go on to necrosis, but, as a matter of fact, there is little direct proof for the rôle of tubercle-bacillus protein in tuberculous pneumonia. The problem has seemed to us, therefore, one in need of more study.

A number of investigators have recorded observations on the results following the introduction of virulent tubercle bacilli into the lungs of tuberculous animals. Austrian and Willis (1) described acute exudative consolidations of the lung produced by intratracheal injection of tubercle bacilli, suspended in blood, into tuberculous rabbits. Morphologically and by X-ray examination the lesions had the character of a noncaseating tuberculous pneumonia. Soper, Sampson and Haskins (2) injected normal and tuberculous rabbits intranasally with emulsions of bovine tubercle bacilli and followed the course of subsequent pulmonary change by study with X-ray films. They found that an early pneumonic reaction followed the aspiration of virulent tubercle bacilli in the lungs of both sensitized and normal rabbits, which was, however, earlier, more intense and more nearly constant in the previously infected animals. Small doses failed to set up a reaction, while large doses (emulsions of

[1] From the Chicago Tuberculosis Institute and the Departments of Medicine and Pathology of the University of Chicago.

2–5 mgm. of dried bacilli) were effective. Resolution also occurred in both groups of animals, more rapidly in the sensitized.

Rich and McCordock (3) have published photomicrographs showing clearly a difference in intensity of the pulmonary cellular response to the intratracheal injection of tubercle bacilli in normal and tuberculous guinea pigs. Their view is that allergy is not necessary for the occurrence of exudative tuberculous pneumonia, but, if present, intensifies the reaction greatly. They state also that they have produced pneumonic exudates, exactly like those resulting from injection of bacilli, by introducing tuberculin intratracheally into allergic animals.

Our studies were directed to the effect on the lung parenchyma of a single constituent of the tubercle bacillus, namely, its specific protein. Four series of guinea pigs were used. In the first two groups, animals infected respectively one and two months previously with human-type tubercle bacilli (H37) were injected intratracheally with a purified tuberculin prepared by Dr. Florence Seibert (4) by ultrafiltration from a culture of H37 on Long's synthetic medium. The amounts used varied from 0.5 to 2 cc., containing approximately 0.5 to 2 mgm. of tuberculin protein. For control, normal guinea pigs were injected intratracheally with the same material, and tuberculous guinea pigs were injected with the uninoculated synthetic medium. The animals were killed after intervals of 24, 48 and 72 hours.

The animals of these series were highly sensitive to tuberculin, but the presence of pulmonary tubercles proved a complicating factor in the histological interpretation of the sections. In a third series of guinea pigs, therefore, a tubercle bacillus of low virulence, not producing pulmonary tubercles (R1), was used for the sensitizing infection. These animals were much less sensitive to tuberculin. The method of injection was the same. In a fourth small series of animals, infected with H37, purified tuberculin protein in aqueous solution was injected directly into the lung through the chest-wall. Similar injections were made into normal animals for control.

RESULTS

The sharp differentiation which we expected in the effect of tuberculin protein on the lungs of normal and tuberculous animals was not realized. In the alveoli of both groups of animals a cellular exudate was produced. It is reasonable to suppose that this was in part due to mucus and bacteria carried down from the upper respiratory passages. Nevertheless a

distinct quantitative difference was noted in the normal and sensitized animals. This was brought out best in the guinea pigs of the first series, infected in the groin with H37, and injected intratracheally a month later with purified tuberculin protein. In the tuberculous animals acute exudative processes, in which both polymorphonuclear and large mononuclear leucocytes took part, were observed around a great many of the terminal bronchioles. In addition to these exudative processes, and not difficult to distinguish from them, frank tubercles were seen. Many of the tubercles appeared to be surrounded by a very active fresh acute process. This we interpreted as a superimposition of the effect of tuberculin on a tuberculous area.

While numerous tubercles were to be found in the tuberculous controls injected intratracheally with the uninoculated synthetic medium, acute exudative responses around the bronchiolar terminations were distinctly less marked than in the case of injections of the tuberculin protein into similar animals. Again, relatively little exudation occurred in normal guinea pigs injected with tuberculin protein. Nevertheless the latter two groups of control animals were not entirely free from pneumonic exudations. The difference was quantitative, not qualitative. In fact, in the third series of animals, in which sensitization was due to R1, and was shown by skin test to be mild, practically no difference in the effect on the normal and tuberculous animals was discernible. In the fourth series of animals injected in the lung directly, distinct interstitial infiltration with cells of inflammation and alveolar exudation occurred, again more marked in the allergic than in the normal animal. In some instances, as might be expected from this rough manner of injection, the picture was complicated by local haemorrhage.

Two other points are worth recording. The exudate caused by intratracheal injection of tuberculin tended to clear up in 48 to 72 hours, leaving the lung in the involved region normal. Second, in no instance was anything resembling caseous necrosis noted. The alveolar walls were often infiltrated with cells of inflammation but never necrotic, although the dose used was in some instances one-fifth of the lethal dose.

It is probable that the picture produced corresponds with the earliest stage of tuberculous pneumonia in man and this stage only. Later those changes dependent upon the multiplication of the aspirated bacilli, including necrosis of the alveolar walls, furnish the specific picture of tuberculous pneumonia.

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SOME BIOPHYSICAL PROPERTIES OF THE TUBERCLE BACILLUS[1,2]

MORTON C. KAHN AND HELEN SCHWARZKOPF

Following the work of DeKruif (1) in 1921–1922 a good deal of attention has been focussed on the phenomena of bacterial dissociation, both from the point of view of pure science and from that of its possible application as part of the mechanism of infection and resistance.

The number of species which have been successfully dissociated prior to this time is a large one, and the literature pertaining to this, as well as to possibly related phenomena, has recently been admirably summarized by Hadley. Among the last to be added to the increasingly long list are the avian and bovine tubercle bacilli, including the BCG strain of the latter. At the present time, as far as we know, there has been no successful dissociation of a culture of the human strain.

In 1928 Petroff (2), working with the A1 strain of the avian tubercle organism, reported that he had been successful in dissociating his stock culture into the R and S types. A little later he dissociated a bovine stock culture (strain B1), and somewhat more recently he has shown that, when the bacillus of Calmette and Guérin is taken from the potato-bile-glycerol medium and grown upon egg, after a number of transfers a very few S colonies make their appearance, but as time goes on these become more and more abundant, and at the same time the entire culture becomes more pathogenic for guinea pigs. In other words, Petroff has been successful also in dissociating the BCG strain of bovine tubercle bacillus. This work on the dissociation of BCG has been recently confirmed in Scotland by Begbie (3); that is to say, in so far as the Scottish investigator had shown that the culture may contain both R and S types of organisms. We have been successful in dissociating a strain of avian tubercle bacillus obtained from the National Tuberculosis Association, as well as a culture of the BCG strain of the bovine organism.

[1] From the Department of Public Health and Preventive Medicine, Cornell University Medical College, New York City. This experiment is part of a group investigation being carried on in conjunction with the Medical Research Committee of the National Tuberculosis Association.

[2] Read in abstract before the Pathological Section at the twenty-sixth annual meeting of the National Tuberculosis Association, Memphis, Tennessee, May 9, 1930.

As Petroff has shown, the R and S types of the A1 avian and of the B1 and BCG bovine strains show a number of distinctive features.

As far as the individual rod is concerned it may be said that the R type is somewhat longer and coarser than the S, while the tinctorial characteristics under acid-fast stain are about the same. The growth-rate of the R type on egg, as well as on the synthetic medium of Proskauer and Beck, is more rapid than that of the S. The topography of the

TABLE 1

Electrophoretic mobility velocities of rough and smooth avian and bovine tubercle bacilli

STRAIN	AVIAN OR BOVINE	ROUGH OR SMOOTH	COLONY NUMBER	VARIATIONS IN SECONDS PER 390 MICRA	AVERAGE MICRA PER SECOND	NUMBER OF READINGS	VOLTAGE PER 3.5 CM.	VOLTAGE PER 1 CM.	AVERAGE M. PER SEC. PER VOLT PER CM.
N. Krumwiede	Avian	R	1	17.2 to 20.0	21.6	10	42	12	1.80
N. Krumwiede	Avian	R	2	17.2 to 22.0	20.5	10	42	12	1.71
N. Krumwiede	Avian	R	3	17.2 to 20.0	20.0	10	42	12	1.66
N. Krumwiede	Avian	R	4	18.0 to 22.0	19.6	10	42	12	1.58
N. Krumwiede	Avian	R	5	14.8 to 20.0	22.3	10	42	12	1.86
N. Krumwiede	Avian	S	1	8.0 to 12.0	39.8	10	42	12	3.30
N. Krumwiede	Avian	S	2	7.2 to 10.0	42.0	10	42	12	3.50
N. Krumwiede	Avian	S	3	10.0 to 12.4	34.7	10	42	12	2.89
N. Krumwiede	Avian	S	4	10.0 to 12.0	34.5	10	42	12	2.88
N. Krumwiede	Avian	S	5	10.0 to 11.6	36.2	10	42	12	3.00
Petroff	Avian	R	1, 2, 3	19.6 to 22.8	18.4	20	42	12	1.53
Petroff	Avian	S	1, 2, 3	10.0 to 12.4	35.4	20	42	12	2.95
Petroff	Bovine	R	1, 2, 3	9.6 to 13.2	35.9	20	42	12	3.00
Petroff	Bovine	S	1, 2, 3	6.4 to 10.0	50.8	20	42	12	4.23

Distance between electrodes of cell, 3.5 cm.

colonies is quite distinct. In the avian and B1 strain of bovine, the S type colonies are smooth, round, domed, glistening, and white-yellow in color, while the R colonies are rough, flatter and more dull. No difficulty is encountered in distinguishing these two types of colonies, although it may be said that on some of the plates intermediate or O types are to be found; that is to say, less smooth than the typical S type and less R than the typical rough. The R colony of the BCG looks a

good deal like a piled-up coil of small intestines, while the S colony is composed of minute, irregular wrinkles, lace-like in structure. In the case of the avian organism Petroff has noted that, when R organisms are grown in medium containing anti-R serum, after 8–10 cultural passages the colonies tend to become S, while when the S types are grown in anti-S serum they tend to become R in character after a similar treatment. The S colonies of all of these three strains form a smooth, homogeneous emulsion in physiological salt solution or distilled water, much as does a colon bacillus or a staphylococcus. The R colonies, on the other hand, are tenacious and flocculate, going into emulsion with difficulty, if at all.

Aside from the above-mentioned features, we have found that there is a measurable difference in the mobility velocity of the R and S colonies when cataphorized either by the technique of Falk or that of Northrup and Kunitz.

As will be remembered, Falk (4) showed that the electrophoretic mobility velocity (potential difference) of diphtheria bacilli varied according to their virulence, the more virulent organisms showing low mobility rate, while those of a less virulent nature gave a higher reading. For pneumococcus, on the contrary, he found that the potential difference is higher the greater the virulence for white mice, and *vice versa*. The sequence of decreasing potentials was shown to be types III, I, II, IV, which follows the decreasing virulence for white mice. This work on the pneumococcus was carried out prior to the isolation of several new types from the erstwhile group IV.

In view of the hypothesis that smoothness of colony may be an indication of virulence, while roughness may be taken as an indication of the reverse, we determined the mobility velocities for the two types of colonies, using the Falk and the Northrup and Kunitz technique. The growths were washed in distilled water just prior to the experiment, and the procedure was adhered to as outlined originally by Falk or Northrup and Kunitz.

Certain sources of error must be taken into consideration when conducting experiments of this nature: *1:* Difference in level of the water-table in the cell makes a single standardization of the cell invalid. As it is impossible to get the identical amount of bacterial suspension in the cell at all times, it is absolutely essential that the cell be standardized for the critical zones prior to each and every individual experiment; otherwise, highly variable and inconstant results will be obtained. *2:* The lower zone of the cell was found to give less variable readings than the

upper zone; therefore the results in these experiments were computed with readings taken only from the lower zone. *3:* Age of culture examined is a third source of error, therefore cultures of identical age and from culture media of identical composition should be examined. When these factors are taken into consideration differences in mobility velocity are apparent for the rough and smooth types of colonies. Whether this difference is correlatable with virulence (in the pathogenic sense), as in the diphtheria group, must perforce await the outcome of animal inoculations at present under way.

Under the conditions of this experiment the average mobility velocity for the rough avian colonies, N strain, was 20.8 micra per second or 1.74 micra per second per volt per cm. For the smooth N strain the average was 37.4 micra per second or 3.11 micra per second per volt per cm. For the Petroff avian strain the average for the rough colonies was 18.4 micra per second or 1.53 micra per second per volt per cm., while for the smooth the average was 35.4 micra per second or 2.95 micra per second per volt per cm. The Petroff bovine strain (B1) revealed an average reading of 35.9 micra per second or 3.00 micra per second per volt per cm. for the rough colonies, while the smooth colonies revealed an average reading of 50.8 micra per second or 4.23 micra per second per volt per cm. In the case of colony no. 3, bovine smooth, there was one reading of 39.0 micra per second. Twenty readings on suspensions from each of 3 other colonies, however, were well within the zone approximated by the average.

Whether these recorded differences in potential difference indicate a difference in virulence remains to be seen. The indications from Petroff's work are that the smooth-colony dissociants show a higher virulence than do the rough. It is interesting, therefore, to note these differences in the electrophoretic mobility velocities of avian and bovine tubercle bacilli from S and R colonies: *not so much at present as an indication of pathogenicity but as an added physical difference between the R and S types.*

No dissociation has been shown for the H37 strain of human tubercle bacillus, but there is a difference in the mobility velocities of the organisms according to the age of the culture. The younger the culture the greater this velocity and *vice versa.* This would seem to indicate that the young cultures may be more virulent, as they more closely approximate the readings gained for the S colonies in the other types of tubercle bacilli. A culture induced to rapid growth by 4-day transfers on Long's

medium revealed an average mobility velocity of 41.7 micra per second or 3.47 micra per second per volt per cm. A 9-day culture gave an average mobility rate of 35.3 micra per second or 2.94 micra per second per volt per cm.

There was then little difference until after 20 days, when the mobility velocity was found to have decreased to 26.8 micra per second or 2.23 micra per second per volt per cm. At the end of 5 weeks the reading was 19.7 micra per second or 1.77 micra per second per volt per cm.

While preparing cultures of human tubercle bacilli for electrophoretic experiments it was noted that even after prolonged centrifugation at high speed there was always a top scum on the liquid (which was found to be composed of tubercle bacilli) as well as the usual bacterial sediment contained in the bottom of the tube. It was thought interesting to determine the electrophoretic mobility velocity of these two components of the contents of the centrifuge tube. Organisms from the top scum gave an average mobility velocity reading of 38.7 micra per second or 3.21 micra per second per volt per cm., while the organisms contained in the bottom of the tube gave a value of 18.7 micra per second or 1.56 micra per second per volt per cm. This would seem to indicate that the top organisms are the youngest of the population of the 23-day-old culture which was used in this experiment, and possibly the more virulent. Animal experiments are now under way to prove or disprove this point.

In view of the distinct dissimilarity of colony morphology, as well as of a number of other features, we thought it advisable to make microcultures of the R and S types in order that the growth-rate, the various phases of colony development and other related experiments could be performed under more critical and controllable conditions. This accordingly was done. The technique employed was essentially the same as used by us in our life-cycle studies of the H37 strain of human tubercle bacillus (5). By using the Chambers micromanipulator and a pipette with an opening of about 2 micra, a number of droplets of the thin suspension of the tubercle bacillus in question were placed on the under side of scrupulously clean cover-slips. These were then sealed off in a hollow-ground slide having a depression of some 2 mm. There were 2 drops of 1.5 per cent agar in the bottom of the depression toward the side, to keep the droplets from drying. Due partially to this precaution and also to the glycerol content of the medium the microdroplets remain intact for several weeks, and the developmental processes may be followed from day to day. The suspensions used in these experiments

contained about 15–30 organisms per droplet. They were prepared from typical R and S colonies on plates showing actual dissociation or from slants of egg medium upon which these dissociants were inoculated. Care was exercised to select typical cultures. In the experiments having to do with the colony-morphology development the organisms were kept on media of identical composition and also planted upon media in which the same formula had been incorporated. Suitable controls for sterility were made. In no case did contamination ensue. It has been our experience with several hundred single-cell and small-group preparations that contamination with this microtechnique is the rare exception, occurring with much less frequency than with the more gross bacteriological methods.

In the microculture with the avian R organisms the period of lag quickly disappears and growth is quite definite at the end of 5 days. The

PLATE 1

FIG. 1. Microdroplet, showing R colony 5 days old. ×175.
FIG. 2. Microdroplet, showing R colony 8 days old. ×175.
FIG. 3. Microdroplet, showing R colony 12 days old. ×175.
FIG. 4. Microdroplet, showing R colony 17 days old. ×175.
FIG. 5. Microdroplet, showing R colony 21 days old. ×175.
FIG. 6. Microdroplet, showing R colony 34 days old. Growth spread almost entirely throughout, medium, showing typical rough configuration. ×175.

entire phenomenon of reproduction is much more rapid for the R type than for the S, as judged by our microcultures. After 8 days of incubation the morphology for the R colony becomes distinct and clear-cut, taking the form of a coarse network of coarse filaments, closely intertwined to form a unit mass. This structure, with its characteristic morphology, rapidly extends throughout the droplet, until after about 30 days the entire microdroplet is covered with the R type of growth. This will be readily seen from the accompanying illustration. Probably due to an attempt at further reproduction and subsequent crowding, the coarser network, as it appears in the droplets of the younger cultures, becomes somewhat more fine, but at no time, even after weeks of incubation, does the R microcolony lose its coarse configuration. Differences between the R and S types are distinct and clear-cut at the end of from 8 to 10 days, in contradistinction to 4 or 6 weeks necessary with the plating method. The limitations with the microtechnique are, however, that, unless one uses only pure cultures of the R and S types to start with,

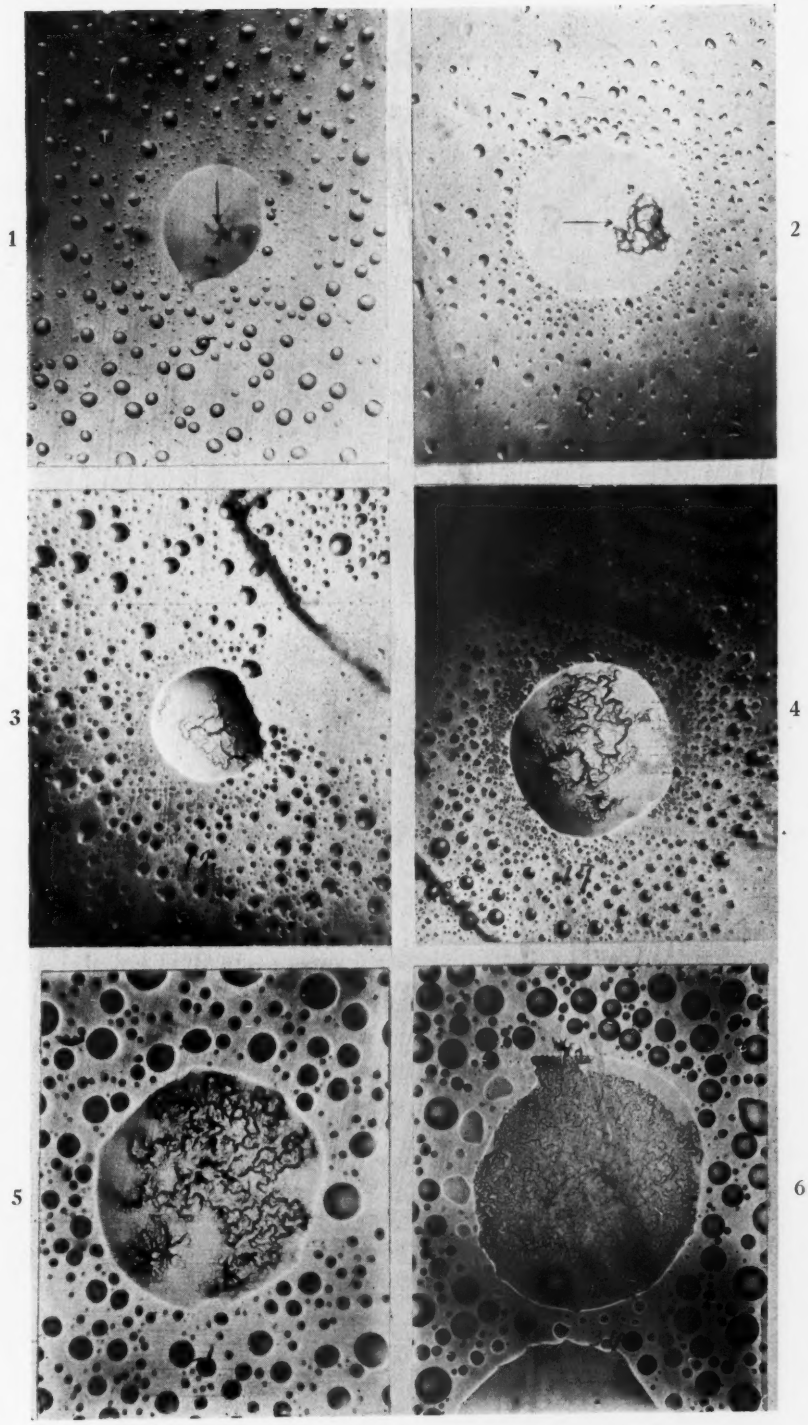

PLATE 1

it cannot be said that the microdroplet does not contain representatives of each type. In using this technique for actual dissociation of an unknown culture, however, it would therefore be necessary to start with single organisms. This is quite feasible as will be shown in a later publication. The morphological development of the S type of colony in the microculture is distinctly different. The tendency to form a homogeneous mass is not so pronounced as in the case of the R, there being a number of free organisms dispersed throughout the droplet until the droplet is entirely covered by growth. The period of lag seems to extend for a longer time and the entire growth process is slower. The organisms which are finer in structure than the R type do not seem to establish themselves as far as reproduction is concerned until after about 8–10 days of incubation, and from that time until the microdroplet is nearly entirely covered with growth the tendency toward forming a

PLATE 2

FIG. 1. Microdroplet, showing S colony 8 days old. ×175.

FIG. 2. Microdroplet, showing S colony 12 days old. ×338.

FIG. 3. Microdroplet, showing S colony 24 days old. Note fine veil-like growth with many single organisms in contradistinction to coarse network of R type. ×175.

FIG. 4. High power of 3. Microdroplet, containing S avian tubercle bacilli 24 days old. Note thin veil-like growth. ×563.

FIG. 5. Microdroplet, showing S colony 31 days old. ×175.

FIG. 6. Microdroplet, showing S colony 39 days old. Growth has spread throughout entire droplet. Compare with R type. ×175.

dense homogeneous mass, as is the case with the R type, seems to be lacking. That there is a network formed by the S organism, however, toward the later stages of the colony developments seems to be true and the structure of this may be readily seen by examining figure 4, plate 2. It will be noted that the structure of this network is much finer in every way than the R colony and a number of free organisms will be seen in the medium. The impression gained is that the growth membrane, if I may call it such, is much less compact than that formed by the R type and much more fragile in every way. After some 35–40 days, depending on the size of the droplet, to a seemingly much greater extent than the R type, the entire surface of the medium will be found to be covered with a growth structure definitely much more regular than that observed with the R microcultures.

Through the kindness of Dr. Petroff we were supplied with some of his anti-R and anti-S avian serum. These substances were made by

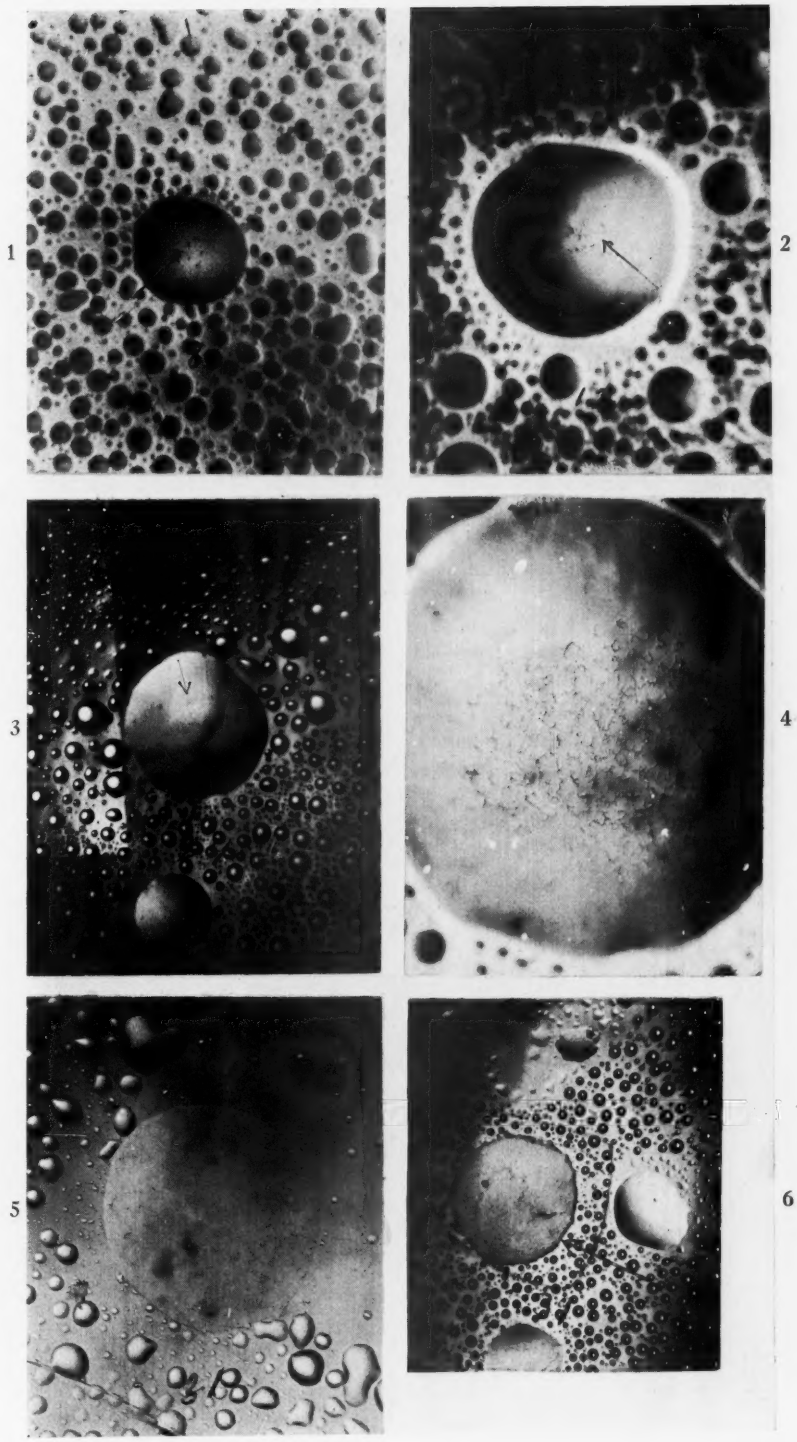

PLATE 2

inoculating goats with graded doses of heat-killed cultures of the organisms. We incorporated some of this serum into the medium used in these experiments in amounts of 10 per cent, and proceeded to make suspensions of R organisms in the R serum and S organisms in the S serum. Microcultures were then made of these suspensions. We were interested to note that in the case of the R organisms in the R serum and the S organisms in the S serum definite inhibition of growth has occurred in both instances. After 45 days of incubation in the microdroplet there is little if any growth on the part of both organisms when planted in their homologous antisera. In many of these droplets no growth at all is apparent. When, however, S organisms are planted in medium containing anti-R serum or the R in anti-S serum, there is no inhibition of growth in either instance. This seems to suggest some degree of serological dissociation when in these respective phases.

A second series of controls, made in human serum which was added to the medium in the same 10 per cent amounts, showed definite enhancement of the growth on the part of each organism.

Microcultures of bovine R and S organisms are now under way. The period of lag of this organism is very extended, seeming to be some 30 days. It cannot be said that growth takes place under the conditions of these experiments until after some 35 or 40 days' incubation. At the present time colonies are not sufficiently developed to state whether difference in the S and R type is to be noted in microcultures. On the plate, however, this difference is quite as definite as is the case with the avian tubercle bacillus.

SUMMARY AND CONCLUSION

Differences in electrophoretic mobility velocities (P.D.) have been shown for the rough and smooth strains of avian tubercle bacilli and also for the rough and smooth strains of bovine tubercle bacilli. No actual dissociation has been proved for the human tubercle bacilli (H37 strain), but there is a marked difference in mobility velocity according to the age of the culture, the younger cultures giving the higher values.

Microcultures have been made and followed of R and S avian tubercle bacilli. Distinct differences in the morphology of the microcolonies formed by these dissociants are early and readily detectable with this technique, and critical examination under oil-immersion magnification may be made, thus materially aiding in studying the mechanism of the

dissociation phenomenon as regards this particular strain of micro-organism.

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THE LYSIS OF TUBERCLE BACILLI IN VITRO

H. J. CORPER[1]

Tubercle bacilli as disease producers occupy a peculiar and distinctly select position in the fields of both bacteriology and pathology in that they possess a slow cycle of growth and reproduction, and cause a disease which also in most cases develops slowly and likewise retrogresses slowly. These facts probably account for the origin of the many variegated conceptions regarding the significance of more or less unimportant factors in the various parts played by the growth and destruction of the bacilli in the body, not to mention that played by resistance, immunity or allergy in determining this. Many of these conceptions have become obviously obsolete and merit no mention here but some are still extant and require further elucidating studies to prove or disprove their significance and existence. Probably of all the studies being pursued in tuberculosis there are none of more practical importance than those concerned directly with the factors determining the growth and destruction of tubercle bacilli in the body because these factors, to put it in simple terms, are decisive in the development of tubercle and its fate. Much information has been obtained regarding this from studies *in vivo* but some of the problems on the growth and destruction of the bacilli can only be elucidated by simplified and well-controlled observations *in vitro*, where confusing counter-reactions can be excluded and the equation guided in one direction with coincident detailed elementary analyses of the factors concerned.

There have been numerous attempts to demonstrate the lysis of tubercle bacilli *in vivo* and although it appears obvious that lysis occurs in some form, technical obstacles and the lack of unquestioned serial or consecutive findings have led to only unconvincing results. In 1910 to 1913 a number of investigators, including Manwaring and Bronfenbrenner (1), who summarized the literature on the subject at that time, believed that they had demonstrated lysis of tubercle bacilli in the peritoneal cavities of tuberculous animals. Their technique and methods were, however, not beyond criticism, part of which they themselves

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pointed out, and their findings were therefore open to doubt. They claimed that isolated peritoneal tissues from tuberculous guinea pigs possessed the power of destroying tubercle bacilli *in vitro*. The duration of their tests, forty-eight hours *in vivo* and eleven hours *in vitro*, with a resultant marked lysis of bacilli recorded for this time, hardly serves a convincing purpose in the light of our present knowledge regarding the biological and chemical integrity of the tubercle bacillus.

In pursuance of the concept of Deycke and Much (1909), which postulates a lipoid lysis of tubercle bacilli, Isabolinksy and Gitowitsch in 1924 (2) and 1927 (3) reviewed the literature on the lysis of tubercle bacilli especially by lipoids and recorded their own investigations. They reported that lipoid-containing substances cause all stages of lipolysis in tubercle bacilli with complete loss of acid-fastness and complete solution of the bacilli. The best results were attained with lecithin, olive oil and green soap. Potassium and sodium salts, as well as alkalies, possessed no bacteriolytic properties. These lipoid-containing substances also caused bacteriolysis in the guinea pig and all stages of lipolysis of the tubercle bacilli were noted to the point of complete solution. In guinea pigs lecithin and codliver oil acted best, while olive oil had less effect and green soap was without action.

More recently Platonov (4) notes that fats of the unsaturated type act "bacteriolytically," retard the growth of tubercle bacilli, and lower their virulence. A little earlier McJunkin (5), and separately Boissevain (6), recorded a loss of acid-fastness in tubercle bacilli treated with alcohol or acetone and oleic acid, with acetone and olive oil, with acetone and liquid petrolatum, and with certain fatty acids of the aliphatic series, in full strength and in emulsion without preliminary dehydration. Boissevain points out that the effect seems to depend on the presence of a long carbon chain (5C) and a COOH group, and to increase with the number of double bonds (degree of unsaturation). McJunkin found the lipase of castor-bean to exert no effect on the tubercle bacillus but suggested that the solvent action is due to a thermolabile enzyme contained in the tubercle bacillus acting only in the presence of undiluted oleic acid. Just how far these experiments can be interpreted concerning conditions pertaining to the body must be left to conjecture at present.

There has always been some confusion in the literature regarding "lysis" of the bacilli and "destruction" in the sense of loss of viability, and Schiller (7) records growing tubercle bacilli within a few days at 37°

in sputum to which had been added an equal volume of 75 per cent glycerol and glucose not to exceed 5 per cent. Without glycerol the bacilli multiply also but after 48 hours they disintegrate (*"gehen sie alle zugrunde"*). He also (8) records complete digestion (*Verdauung*) of tubercle bacilli by yeast within 8 hours.

About the same time Richet and Hauduroy (9) found that positive sputa in three out of a total of 29 cases revealed a complete disappearance of tubercle bacilli, while in five there occurred a notable diminution within 2 to 10 days at 37°C. When peptone water, serum, etc., were added, a diminution was noted in 25 of 50 sputa and in 7 there was a complete disappearance of bacilli. The disappearance of the bacilli was due to a thermostable principle since sterilization of the sputum augmented the phenomenon. The next year Richet (10) in a brief article reported that human tubercle bacilli mixed with aseptic liver, spleen and muscle disappeared rapidly.

On the other hand, the resistance of tubercle bacilli to disintegrative action of various kinds is commonly noted in the literature and is especially strikingly brought out in the report of Burns (11) who was able to find morphologically unchanged tubercle bacilli in a tuberculous sputum twenty-two years old. Cultures and guinea-pig inoculations were, however, negative.

Webb, Ryder and Gilbert (12), working with tuberculous lymph nodes, found a loss of viability of tubercle bacilli in incubated nodes but noted no noticeable changes in the shape or staining reaction of the bacilli even after incubation for 43 days. Even after nine weeks of implantation in a new host the bacilli still appeared normal though calcification was occurring.

These observations were verified by Corper, Lurie and Kretschmer (13), and attempts to demonstrate lysis of tubercle bacilli in guinea pigs injected with living and heat-killed bacilli only proved futile (14),—with living bacilli because of the progression and the fatal issue of the disease, and with dead bacilli because of extinction by pus-formation before evident visible changes had set in.

Regarding the enzymatic destruction of tubercle bacilli, a recent interesting article by Day and Gibbs (15) merits mention. They found that tubercle bacilli were killed by the pancreatic juice from dogs but there was no evidence obtained of a dissolution of the cells or loss of acid-fastness. Pancreatic secretion activated with enterokinase was no more bactericidal than the normal juice, while pancreatic juice, diluted with salt solution or bile, or made acid, was ineffective against bacteria.

The study to be reported below is the culmination of an attempt, extending over many years of fruitless endeavors, to note lysis of tubercle bacilli and part of a study to simplify the method of growing small numbers of tubercle bacilli in pathological materials and from such materials, and to avoid pitfalls in pursuing the latter tests. In earlier studies (16) it was noted that fully-grown cultures of both human and bovine tubercle bacilli remain viable in the icebox or in the incubator only for eight to sixteen months, and that in growing on culture media tubercle bacilli undergo a regular metamorphosis—cytomorphosis (14)—which can be correlated with the time- and growth-curve of the bacilli, the period of early (accelerating) growth being identified through the presence of a large number of long, filamentous, uniformly staining, acid-fast bacilli, while the period of adult (phase of negative acceleration) growth is identified through a preponderance of moderately long bacillary forms with and without metachromatic granules, and the senescent cells consist of uniformly acid-fast coccoid and short bacillary forms.

Several years ago it was found that 6 per cent sulphuric acid (17) could be used to efficiently destroy rapid-growing contaminators and acid-fast bacilli without detrimental effect upon tubercle bacilli and that in blocks of tissues sterilized with this acid the tissue autolytic enzymes were not destroyed but their action was inhibited by potato-cylinder culture media (18). Tubercle bacilli contained in small blocks of tissue sterilized with sulphuric acid lost their viability within three to ten days as a result of the action of the autolysates formed by such tissues kept in 6 per cent glycerol water at 37°C. At the time that the latter study was being pursued all the autolyzed tissue blocks, as well as controls, were submitted to microscopic examination, after staining with haematoxylin and eosin and also after staining with carbol-fuchsin with a method which yielded good results with sections of tissues which had not been submitted to autolysis at 37°C. In spite of the fact that the controls in some cases were fairly heavily laden with tubercle bacilli and were definitely positive in stained sections, the tissues which had been placed at 37°C. in 6 per cent glycerol water for only a few days, after sterilizing with 6 per cent sulphuric acid and washing with sterile 0.9 sodium-chloride solution to remove the sulphuric acid, were consistently negative for acid-fast bacilli.

The technique used originally consisted, briefly, of staining the bacilli in the paraffine-embedded sections for 15 to 25 minutes with steaming carbol-fuchsin, decolorizing with 10 per cent nitric acid and counterstain-

ing with iron-haematoxylin, clearing, and mounting in balsam. Believing that possibly the iron-haematoxylin treatment was unsuitable for preserving the color in the bacilli, another technique was used with equally poor results. This method, the Ziehl-Neelsen-Gabbett method, consisted of staining the sections with carbol-fuchsin, and counterstaining and decolorizing for one minute with Gabbett's methylene-blue solution, clearing and mounting in balsam. This method also was efficient for tissues that had not been autolyzed but was valueless with the tissues incubated at 37°C. for just a few days, giving negative results, whereas stained smears proved positive. In spite of numerous control tests that were run in an attempt to solve this difficulty, no explanation was found for the effect of the autolysis, as a result of incubation at 37°C., upon the inability to stain the tubercle bacilli in Zenker-fixed paraffine-embedded sections of the tissues.

A number of times within the past ten years futile attempts were made to study the effect of tissue autolytic enzymes upon suspensions of tubercle bacilli by using the usual antiseptics, such as sodium fluoride, sodium benzoate, toluol and chloroform, used in studying tissue autolysis, and the tests were carried out at incubator and room temperature for a period of several months' observation, but the irregularity with which the bacilli were found in consecutive smears and persistent positive findings with ground tissues and virulent tubercle bacilli led only to discouragement in following this lead for information on the enzymatic lysis of tubercle bacilli. Frequent contamination of the mixtures when using these antiseptics at incubator temperature also made all findings with these tests extremely doubtful so far as definite and conclusive findings were concerned.

The difficulty of using fresh, aseptically removed organ tissue, and keeping them sterile for several months of testing at incubator temperature, also proved insurmountable in numerous earlier trials to study the *in vitro* lysis of tubercle bacilli by tissues and tissue enzymes. It was with gratification, therefore, that it was found that 6 per cent sulphuric acid, 3 per cent hydrochloric acid and 5 per cent oxalic acid, in about equal volume, added to tissues and incubated for 30 minutes, would serve to destroy contaminators without appreciably harming the tubercle bacilli contained in these tissues. After attempts to stain the tubercle bacilli in sections of autolyzed tissues, obtained from animals that had received moderate amounts (about 0.001 to 1 mgm.) of fine suspensions of tubercle bacilli intravenously, proved of little avail, it was decided

to inject large amounts of fine suspensions of virulent human tubercle bacilli directly into the spleen, liver and kidney by way of the splenic, hepatic and renal arteries, and to examine the tissues for tubercle bacilli, before and after autolysis at incubator temperature, both in section and in smear and to utilize 6 per cent sulphuric acid in equal volume for 30 minutes at 37°C. for sterilizing small blocks (2 x 5 x 5 mm.) from the various organs and removing the acid by means of ten volumes of sterile 0.9 sodium-chloride solution. Dogs were used in these experiments for several reasons: they are of sufficient size to ensure satisfactory arterial organic injections; they easily survive a general anaesthetic and large injections of tubercle bacilli; and sufficient tissues of the various organs are available for extensive tests. The operations were performed with strict aseptic precautions, although it is now realized that this was not absolutely essential when sterilizing the tissues with sulphuric acid before incubation. Since the suspensions of bacilli used for injection were necessarily large amounts, due precautions were taken to obtain, by careful grinding, as fine suspensions as possible. The amounts injected into the arteries of the several organs ranged from about 0.8 to 1.0 gm. of bacilli and these were suspended in about 20 to 30 cc. of sterile saline solution. After the injection the dogs were allowed to live for from five to eight hours, when the desired organ was removed aseptically and cut into small blocks about 1 to 2 mm. thick and about 3 to 5 mm. in width. These blocks were then treated with the sulphuric-acid reagent and washed, and were then transferred to small sterile corked bacteriological test-tubes (0.5 x 3 in.), a few drops (3 to 6) of sterile 6 per cent glycerol water was added, the cork was impregnated with paraffine, and the tubes in covered tin cans were placed in the incubator at 37°C. Specimens, as controls, were immediately taken to make smears and sections, and others were kept at room temperature. An exhaustive method for recording was used in making the counts presented in the tables, but, since these gave no more information than the figures recording the total number of bacilli found, only the latter are recorded in the tabulations. In evaluating the figures resulting from the direct organ injection it must be remembered that not all the bacilli injected into the artery were necessarily retained in the organ in question, and that many probably passed into the general circulation. The results of some of these experiments with smears made from the dog's spleen, liver and kidney, submitted to incubation at 37°C. for periods up to six months, are recorded in table 1.

It is to be noted from the results recorded in table 1 that tubercle bacilli contained in the spleen, liver and kidney of the dog as a result of intraärterial injection undergo a gradual change at incubator temperature, resulting in the loss of staining capacity for the usual carbol-fuchsin stain as tested in the heat-fixed smear. Tubercle bacilli in tissues kept at room temperature suffered no appreciable change paralleling those kept at incubator temperature within the experimental period of observation recorded. In order to prevent possible loss of bacilli resulting from changes consequent to autolysis which might make the tissues unsuitable for fixing to the micro-slide, albumin fixative was used throughout these

TABLE 1

The lysis of virulent human tubercle bacilli in tissue blocks sterilized with sulphuric acid

DESCRIPTION OF TISSUE	PERIOD OF INCUBATION AT 37°C. OF TISSUE BLOCKS IN GLYCEROL-WATER						
	Control	1 week	2 weeks	1 month	2 months	4 months	6 months
Spleen from dog that received 0.9 gm. of bacilli into splenic artery.....	205*	164	231	34	64	0†	0
Liver from dog that received 1 gm. of bacilli into hepatic artery.....	284	174	52	4	5	6	0
Kidney from dog that received 0.9 gm. of bacilli into renal artery.....	324	148	297	43	7	0	0

* Number of bacilli in 100 oil-immersion fields are recorded in the tabulation. The results of carbol-fuchsin-stained smear examinations are given. Stained sections made on all the tissues proved too unsatisfactory to be of value in these tests.

† The glycerol-water in which the block was suspended was also negative after this time and fresh tissue added to aid in obtaining heavy smears did not change the findings, while controls kept at room temperature over six months were still positive.

tests and, in addition, duplicate specimens were mixed with fresh tissues to ensure the preparation of sufficiently heavy smears and to avoid the possibility of washing off any of the autolyzed tissue material while performing the technical staining procedures.

Having thus been assured that there is a lysis of tubercle bacilli in autolyzing tissues, which occurs over a period of about two to four months at incubator temperature in tissues infected *in vivo*, it seemed advisable to determine whether fresh and heat-killed tubercle bacilli mixed with ground tissues *in vitro* would suffer similar changes at incubator temperature. Accordingly fresh dog spleen and liver were ground through a fine-mesh sieve and the tissue-mush was sterilized by treating

it with an equal volume of 6 per cent sulphuric acid and kept at 37°C. for thirty minutes with occasional shaking to ensure penetration of the acid into the tissue and thorough sterilizing, after which the acid was diluted with ten volumes of sterile 0.9 per cent sodium-chloride solution and the supernatant fluid decanted after centrifugation. To this acid sterilized tissue was added a few drops of sterile 6 per cent glycerol water and 0.1 mgm. of fresh or heat-killed tubercle bacilli in fine and uniform suspension per cubic centimetre of mixture. The heat-killed bacilli were prepared by placing the suspension in a boiling water-bath for about one hour. After mixing the acid sterilized ground tissues and bacilli thoroughly, control smears were prepared, and the remainder of

TABLE 2

Lysis of virulent human tubercle bacilli added to ground tissues sterilized with sulphuric acid

BACILLI PER CC. ADDED TO GROUND TISSUE FROM DOG	PERIOD OF INCUBATION AT 37°C. OF MIXTURE OF BACILLI WITH GROUND TISSUES IN GLYCEROL-WATER					
	Control	1 week	2 weeks	1 month	2 months	3 months
Ground spleen + 0.1 mgm. fresh tubercle bacilli	264*	234	80	20	9	0
Ground spleen + 0.1 mgm. boiled tubercle bacilli	209	147	109	23	0	0
Ground liver + 0.1 mgm. fresh tubercle bacilli	184	153	65	4	0	0
Ground liver + 0.1 mgm. boiled tubercle bacilli	186	131	29	2	7	0

* The number of bacilli recorded are given for 100 oil-immersion fields found in carbol-fuchsin-stained smears.

the mixture, in the tubes closed with paraffined corks, was placed in covered tin cans, which were put in the incubator, smears stained with carbol-fuchsin being prepared from the mixtures at regular intervals. The results in number of acid-fast bacilli found per hundred oil-immersion fields at intervals up to three months are recorded in table 2.

The results recorded in table 2 indicate that both fresh and heat-killed tubercle bacilli suffer a loss of morphological integrity, as gauged from their ability to be stained by the carbol-fuchsin technique, when incubated at 37°C. in mixture with sulphuric-acid sterilized ground spleen or liver tissue of the dog. There is a gradual diminution of the number of acid-fast bacilli found in the mixture of tissue and tubercle bacilli to the point of absence in about one to two months. In all these experi-

ments there were noted no decided morphological changes in the bacilli during the process of lysis, but there appeared to be merely a gradual digestion to which no one part of the bacillus seemed to be more susceptible than the others. Thus the forms generally found to predominate at any one stage of the process were almost identical with those existing at the initiation of the experiment. This was in contrast to the changes noted during the cytomorphosis of tubercle bacilli occurring on media during the various periods of development and growth of the cultures to final loss of viability.

SUMMARY AND CONCLUSIONS

The sulphuric-acid sterilization of tissues offers a method for studying the effect of autolytic tissue enzymes upon tubercle bacilli in producing sterile tissues in which the usual rapid-growing microörganisms have been destroyed and in which the tubercle bacilli have not been appreciably harmed.

Tissue blocks (dog's spleen, liver or kidney) containing tubercle bacilli, sterilized by means of sulphuric acid, and kept at incubator temperature after the addition of glycerol-water, reveal a diminution of acid-fast bacilli with complete disappearance within about two to four months, while the same tissues kept at room temperature reveal no such changes within this time.

Ground tissues (dog's spleen or liver), sterilized with sulphuric acid, to which suspensions of fresh or heat-killed tubercle bacilli in glycerol water have been added, reveal a gradual disappearance of the acid-fast bacilli within about one to two months, at incubator temperature.

Tubercle bacilli, incubated at 37°C. in tissues sterilized with sulphuric acid, lose their viability within three to ten days as a result of the formation of toxic autolysates (18), and undergo a loss of morphological integrity which is evident from the disappearance of acid-fast staining properties, during which there are to be noted no actual morphological changes, such as are seen coincident with the cytomorphosis noted during reproduction and growth on culture media. It appears evident from these studies that, when lysis of tubercle bacilli begins, growth is interrupted and at a stage attained at the time of initiation of lysis, and the only changes coincident with lysis are a dissolution of the cell, possibly with a slight swelling and pyknosis, paralleling that occurring in the nucleus of tissue cells undergoing autolysis or digestion and necrosis.

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SOME RELATIONS BETWEEN IMMUNITY AND BIOCHEMISTRY IN TUBERCULOSIS

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Immunity can be due to the presence of substances that kill pathogenic microörganisms or to physical and chemical conditions that make growth or multiplication impossible for them. In the case of tuberculosis the existence of antibodies that destroy the tubercle bacillus seems extremely doubtful. We must rely for our explanation of resistance on changes in metabolism that make living conditions for the bacillus less favorable. Numerous indications of the process by which human beings resist tuberculosis may be found in clinical and laboratory experience. Tuberculous lesions are hardly ever found in the muscles, with the rare exception of the heart-muscle, but frequently in the lungs and lymph nodes, and in the spleen in laboratory animals. Diseases like diabetes and influenza have an unfavorable effect on the course of tuberculosis, but cancer is said to be antagonistic to the development of tuberculous lesions. Complete rest is the best cure for tuberculosis while muscular exertion and starvation are harmful.

It is possible that the metabolism is changed by absolute rest in some way which diminishes the food-supply available for the tubercle bacillus, while muscular action, starvation, diabetes, etc., may increase it. The tubercle bacillus needs for its growth oxygen, a source of carbon, preferably glycerol, a source of nitrogen, phosphorus, magnesium, potassium, perhaps iron, and a surface to grow upon.

The tubercle bacillus usually grows on the surface of our culture medium. It has been suggested that this is caused by its need of oxygen. That this is not the case is shown by the following experiment: If a small piece of tuberculous tissue is put in a tube containing a mixture of equal parts of blood-serum and peptone water, growth occurs on the surface of the tissue that is covered by the liquid medium (1). A similar phenomenon occurs in the growth in coagulated plasma. If a few tubercle bacilli are mixed with liquid rabbit-plasma, and the plasma is then allowed to coagulate, separate colonies appear after a few weeks through-

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out the coagulated plasma. Colonies in the depth of the medium do not occur when serum is solidified with agar instead of fibrin; in that case growth appears exclusively on the surface (2). On liquid serum a scanty growth appears on the surface and also on the interface of the glass walls and the culture medium; the medium itself, however, remains clear. During an investigation of the changes that occur in plasma during coagulation it appeared that a suspension of kephalin provided an excellent surface for the growth of tubercle bacilli. If a suspension of kephalin is added to Long's medium, the tubercle bacilli grow throughout the medium instead of on the surface only. This action of kephalin is not specific, since lecithin has the same effect; suspensions of starch and glycogen also favor the growth of tubercle bacilli, but to a less extent than the two lipoids. Agar and cholesterol are without action.

Several explanations are possible of this effect of the surface on the growth of the tubercle bacilli. It could be explained by Warburg's theory of surface oxidation (3), especially in view of the circumstance that small amounts of iron favor the growth of tubercle bacilli. The addition of potassium cyanide or pyrophosphate to a medium containing kephalin does not inhibit growth; this seems to exclude the possibility of surface oxidation. A second possibility is that the nutritive substances are concentrated on the surface. Among the substances necessary for growth of the tubercle bacillus, glycerol is the only one that lowers surface tension and can be accumulated in the surface. All our data for surface tension have been measured for the air-water interface, and do not apply to the lecithin-water or starch-water interfaces. In the case of lecithin and kephalin the matter is further complicated by the fact that both serve as a source of carbon and phosphorus for the tubercle bacillus. A third possibility is that the tubercle bacillus obtains some of the energy necessary for the synthesis of its body substance from the capillary action at the surface, in the same way as Baly suggested that plants obtain energy for the synthesis of carbohydrates (4).

It is impossible at present to choose between these theories. The fact remains that lecithin and kephalin, which favor the growth of the tubercle bacilli, are universal cell constituents. The amount of lipoid in a given organ may influence its susceptibility to tuberculosis; it is however worthy of note that the brain which is richest in lipoid is not very frequently the site of tuberculous lesions.

Corper has studied the availability of oxygen in different organs, and has found that a definite relation exists between the oxygen tension and

the velocity of growth of tubercles after the intravenous injection of tubercle bacilli (5). The growth is fastest in the lung and slowest in the liver which receives large amounts of venous blood. He suggests that exercise and starvation increase the hydrogen-ion concentration of the blood and consequently the ionization of oxyhaemoglobin, and thus increase the oxygen supply of the tubercle bacilli. He also showed that optimum growth of tubercle bacilli occurs at the oxygen tension of alveolar air (100 mm.) and decreases with diminishing oxygen tension, to stop entirely at an oxygen tension of 0.8 mm. It seems quite probable that an abundant supply of oxygen favors the growth of tubercle bacilli, but the difference between the oxygen tension of venous blood (35 mm.) and the tension of 0.8 mm., where all growth stops, is too large to attribute more than a minor influence to the change in oxygen tension due to a small change in the pH of the blood-serum.

The serum always contains sufficient phosphates for the growth of the tubercle bacillus. In addition to this lecithin and kephalin can serve as an adequate source of phosphorus.

Magnesium and potassium are both necessary for the growth of tubercle bacilli; the serum-content of these elements varies but little and seems incapable of influencing the development of tubercle bacilli in one direction or another. According to Zwaardemaker radioactive substances may replace potassium in several of its activities in the animal body, notably in its influence on the normal heart-beat. Radioactive substances cannot replace potassium in the culture of tubercle bacilli (6). If it were possible to substitute, for instance, radium for potassium in the animal body, we might make life impossible for the tubercle bacillus. It seems however improbable that radium could take over all the functions of potassium in the body; for instance, its action as base in the red blood corpuscles.

Glycerol must be considered in the first place as a source of carbon. Little is known about the variations of free glycerol in the blood-serum; if this were the only source of carbon for the tubercle bacillus, an effort might be made to control it by excluding it from the diet. However, lecithin can supply all the glycerol that the tubercle bacillus needs and is abundantly present in all tissues.

Only the source of nitrogen remains to be discussed. The nitrogen from lecithin and kephalin cannot be used by the tubercle bacillus. The serum proteins cannot supply nitrogen; if we precipitate the serum proteins with magnesium sulphate, dialyze them, and add them as sole source of nitrogen to a synthetic medium, no growth occurs. The serum

ultrafiltrate, on the other hand, can usually serve as a source of nitrogen. The greater part of the nonprotein nitrogen consists of urea, uric acid and creatinin, none of which can serve as a source of nitrogen. There remain to be considerd the more or less undetermined amino acids and ammonia. Some amino acids, glycocol, leucine, alanine, etc., can supply nitrogen to the tubercle bacilli; others, such as tyrosin, phenyl alanin, and tryptophane, cannot. No accurate methods are available to distinguish between small quantities of amino acids such as are present in the blood. It is at present impossible to decide if the favorable effect of complete rest, for instance, may be due to a decreased percentage of favorable amino acids.

According to Long's hypothesis phenyl-alanine, etc., is not available for the tubercle bacillus because of the toxicity of the phenyl ring after the amino group has been removed (7). This raises the question whether amino acids do not function simply as a source of ammonium ions. In my experience growth of tubercle bacilli on a medium containing only amino acids as a source of nitrogen is invariably accompanied by the appearance of ammonia in the medium. The tubercle bacillus contains a ferment capable of splitting off ammonia from α-amino acids. The ammonia is then utilized by the bacilli, which grow excellently on a medium containing only ammonium salts as a source of nitrogen. Blood-serum and tissues, with the exception of the kidneys, contain very little ammonia; according to some authors it is even absent from the blood-serum. Usually the value of 0.05 mgm. ammonia N per 100 cc. of blood is given. It follows that the ammonia, as soon as it is split off by the tubercle bacilli, is carried away by the ammonia-free lymph, which leaves the tubercle bacillus in a perpetual state of nitrogen starvation.

Unfortunately another source of ammonia exists. Freshly drawn blood is practically free from ammonia; after standing at room temperature for 24 hours, taking precautions against the absorption of ammonia from the air, the amount may increase fifty times. If we centrifugate the blood immediately after obtaining it, and keep the plasma and corpuscles separately, the ammonia content of the plasma remains constant but that of the corpuscles increases. The ammonia content of red blood corpuscles free from leucocytes remains constant, and we are forced to conclude that the source of the ammonia must be sought in the leucocytes. The ammonia content of plasma plus lymph nodes may show an increase or may remain nearly constant; the addition of an exudate containing principally polynuclear leucocytes has only a slight effect on the ammonia content of the plasma, but the addition of

splenic tissue causes an increase to the same value as found in whole blood after twenty-four hours. Since the spleen contains a large percentage of monocytes it seems probable that they are responsible for the formation of ammonia in the blood. The increase in ammonia after the addition of lymph nodes and exudate may be due to the fact that it is not possible to free them completely from monocytes. The predilection of the tubercle bacillus for the monocyte can now be explained because it is the only place where it is assured of a supply of nitrogen.

The veins from the extremities contain less ammonia than the arteries leading to them (8). This may be caused by the synthesis of adenylic acid from ammonia and inosinic acid which has been described by Embden (9). The muscles contain consequently even less ammonia than the rest of the body and are remarkably free from tuberculous lesions. As soon as they are removed from the body, postmortem ammonia formation sets in and they become an excellent medium for the culture of the tubercle bacillus.

Urine always contains relatively large amounts of ammonium salts, although the blood is practically free from them. If we assume that the kidney and the monocytes form their ammonia from the same mother substance, it follows that those conditions in which we find an increased excretion of ammonia in the urine are those that favor the growth of tubercle bacilli. Actually we find increased ammonia excretion after muscular exertion, during starvation and in diabetes, all conditions which favor the development of tuberculosis. This increased ammonia production is the result of increased acid production, to which Corper drew attention as a possible source of increased oxygen supply. However, the tubercle bacilli in the lung have the optimum amount of oxygen available, with a large factor of safety, but are on the edge of nitrogen starvation from which they are only separated by the thickness of a monocyte. Under these conditions a small change in available nitrogen may make a great deal of difference to the tubercle bacillus.

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THE EPITHELIOID CELL[1,2]

R. S. CUNNINGHAM AND EDNA H. TOMPKINS

Before the supravital method was used in the study of tissue cells, the epithelioid cells of tuberculous lesions were recognized largely by the manner in which they were arranged, as, for instance, in characteristic tubercles. By the use of the supravital stain (1), it was found that in tuberculous tissues the characteristic cell was a large mononuclear with a large number of very fine neutral-red vacuoles; this cell was identified as the epithelioid cell. Thus the use of the supravital method of study made it possible to recognize this particular type of cell even when entirely independent of any especial morphological arrangement or distribution.

Reference to the literature will demonstrate that much confusion has arisen as to the types of cells occurring in the lesions in tuberculosis, syphilis, foreign-body reactions and various other conditions. The results which we have obtained by means of the supravital method of study suggest that this great group of reactions may, with profit, be approached from the point of view of the specific characteristics of the individual cells most commonly present in each condition. While we are primarily interested in the occurrence of the epithelioid cell, as defined above, other cells of the tissues in these reactions must be considered.

As mentioned above, Cunningham, Sabin, Sugiyama and Kindwall (1) found that the characteristic cell of tuberculous tissue was considerably larger than the average monocyte and was often multinucleated. It contained a characteristic rosette when stained with neutral red. This rosette was situated in the *Hof* of the nucleus, and was usually of such size that it occupied the major portion of the cytoplasmic space. It was composed of innumerable fine droplets of dye which were very even in size. Large droplets were seldom present, and it was believed that this fact indicated a lessened phagocytic capacity on the part of the cell. Fine droplets of fat were frequently found in the peripheral part of the

[1] This work was assisted by a grant from the National Tuberculosis Association.

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cell. The size of the rosette, and the fineness and evenness of the droplets of dye which formed it distinguished this cell morphologically from the two highly phagocytic cells of the connective tissues, the monocyte and the clasmatocyte. The authors also found great numbers of monocytes in association with epithelioid cells in tuberculous tissues. They observed all stages of transitions, in the type of staining, from that characteristic of the monocyte to that characteristic of the epithelioid cell. They found that the Langhans giant cells contained rosettes similar to those in the epithelioid cells. On the basis of these findings, they formulated the concept that epithelioid cells develop from monocytes as a result of a tuberculous infection; that epithelioid cells are unable to digest the bacilli which had been previously ingested; that intracellular multiplication of the bacilli takes place; and that abnormal cellular division results in the formation of giant cells.

Sabin, Doan and Forkner (4) injected rabbits with fractions of tubercle bacilli obtained by chemical methods. They found that the injections of the phosphatide fractions were followed by massive accumulations of typical monocytes, epithelioid cells and giant cells of the Langhans type in the areas of injection.

Cunningham, Tompkins and Lawrence (2) studied fresh scrapings of the subcutaneous tissues of guinea pigs after the tissues had been injected with solutions of yellow phosphorus in olive oil. There were always present in the scrapings great numbers of degenerate cells which were filled with fat, and which did not stain with neutral red. Mixed with these, however, were also great numbers of monocytes, epithelioid cells and Langhans giant cells which were entirely similar to the cells found in scrapings obtained from tuberculous animals. Clasmatocytes were also present in excess of the normal.

Wright (5) injected nitrogen, oxygen and carbon dioxide, respectively, into the subcutaneous tissues of guinea pigs, and made supravital studies of scrapings taken from the experimental areas at the time of autopsy. Many of the cells present in the scrapings resembled those from tuberculous tissues. The monocytes were far in excess of the number to be found in normal connective tissue, and in addition there were typical epithelioid cells and Langhans giant cells. The reaction was more massive and sustained after the introduction of nitrogen than after that of oxygen or carbon dioxide, but it was quite definite in all cases. Fixed tissues of these lesions showed characteristic tubercle-like arrangements of large mononuclear cells.

It is obvious from the experiments outlined above that, in accord with the older concepts of pathology, stimuli other than tubercle bacilli can inaugurate the production of epithelioid cells, even when defined in the terms of the more specific morphology permitted by the supravital technique. In an effort to penetrate the basic factors underlying this stimulation, many substances have been introduced into the subcutaneous tissues of guinea pigs, and at various intervals after injection the animals have been sacrificed, and the tissues studied both supravitally and in fixed preparations. Almond oil, poppy-seed oil, olive oil and mineral oil have been injected into the tissues, both in the undiluted state and as emulsions in physiological saline. The injection of these oils was invariably followed by a local accumulation of the same types of cells as had been found in tuberculous tissues and in the tissues following the introduction of the phosphatide fractions, of phosphorus in oil, and of gases. Subcutaneous injections of suspensions of agar and droplets of mercury were also followed by similar reactions. Granulocytes and clasmatocytes were more conspicuous in number after the injection of solids than after that of gases and oils, but nevertheless, there were always many monocytes, epithelioid cells and Langhans giant cells present. These results have been qualitative in all cases.

The substances which have been used to stimulate the production of monocytes and clasmatocytes, as well as of epithelioid cells and giant cells, are completely unrelated chemically. That this reaction is not specific for tubercle bacilli is obvious. This reaction of the tissues was characterized not only by accumulations of the normal phagocytic cells of the connective tissues, the monocytes and the clasmatocytes, but by morphological indications of changes in the physiology of these actively phagocytic cells of a nature which seemed to represent a depression of their functions and to result in stages leading toward their degeneration. Cells were found in great numbers, which normally should have had the capacity of storing large aggregates of dye, but which contained only very fine dye-filled vacuoles. The normal capacity to undergo division seems to have been injured so that in many instances the nuclei underwent division without division of the cytoplasm, and giant cells were formed. Ultimately they degenerated, in the course of which they became filled with fat.

While the substances capable of initiating these changes are evidently not related chemically, it seems probable to us that the reaction cannot be explained entirely on the basis of the introduction of a foreign

substance into the tissues, and that the character of the substance introduced in some way determines the reaction. We have found that subcutaneous injections of saline suspensions of lecithin also result in local accumulations of large mononuclear cells. In these experiments, however, the large mononuclear cells showed, in general, the opposite morphological characteristics from those of the epithelioid cell. Their phagocytic capacity was markedly increased, as shown by very large and rather even-sized deposits of dye, which completely filled the entire cytoplasm. They rarely contained fatty droplets. They developed to enormous cytoplasmic size, and they gave little evidence of degeneration. Multinucleated cells have been very rarely found. The stimulation to the accumulation of mononuclear phagocytic cells was as great as in the instances in which the substances injected gave rise to the production of epithelioid cells, but, judging from the morphological characteristics, the physiological activity of the cells produced was utterly different. Morgan (3) has found that the scrapings from syphilitic lesions, produced experimentally in rabbits, also contained many phagocytic mononuclear cells which were characterized by an increased power of phagocytosis, an increase in the ratio of cytoplasm to nucleus, and a diminished tendency to accumulate fat.

It would seem that many substances, when introduced into the subcutaneous connective tissues, are capable not only of producing accumulations of large mononuclear cells, but of modifying the morphology and physiology of these cells in different ways. In one direction the substances introduced seem to increase some of the physiological activities of the cell. The phagocytic capacity is increased; cellular division appears normal; and degeneration tends to take place without the accumulation of extensive deposits of fatty granules. The cells found in syphilitic lesions and those which result from subcutaneous injections of lecithin are, in general, of this type. On the other hand, the substances which stimulate the production of epithelioid cells and of Langhans giant cells apparently act by a depression of physiological activities in such a manner that the phagocytic capacity becomes decreased and modified; cellular division becomes abnormal (so that multinucleated forms result); the metabolism, as indicated by the accumulation of fat, becomes disturbed; and fatty degeneration takes place. The exact nature of these differences in the degeneration in the two types of cells is not yet evident. That it is connected with the metabolism of the cell seems likely. Where the material introduced into the tissues is of such

a nature as to interfere with the normal metabolism of the cell, it is probable that epithelioid cells are produced. This seems true, whether the interference acts from within or without the cell; that is, whether the disturbance to the metabolism is due to direct toxic effects upon constituents of the cell, or to the interference with the supply of substances necessary for the nutrition of the cell.

These are merely hypotheses, but they present a different approach to cellular physiology and pathology than has previously been possible, and they open the way to a new study of the differences in the reactions of the tissues to various stimuli.

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A DEMONSTRATION THAT THE RESERVE SUPPLY OF MONOCYTES IS INCREASED IN TUBERCULOUS ANIMALS[1]

J. T. GEIGER[2]

It has long been known that, when certain substances are exhibited into the animal organism, there is produced a marked leucocytosis in the peripheral circulation. The classical example is, of course, the leucocytosis of acute infection, in which the rise may be marked and is often sustained for a considerable period of time. Recently, it has been shown by Doan, Zerfas, Warren and Ames (2) that certain products of nucleic acid, particularly sodium nucleinate, will produce a leucocytosis as high as 120,000 cells per cubic millimetre of blood in the rabbit. It is of importance to note that a leucocytosis of this type is different in character, as well as in extent, from that obtained by Garrey and Butler (3) (4). These authors have demonstrated that leucocytoses can be induced by exercise and by other means within physiological limits. This latter type of leucocytosis is probably one of distribution alone and is not, to any marked degree, the result of a true emigration. Thus it seems possible to distinguish two distinct types of storage; one of immature cells which are so close to the adult stage that they can be promptly transformed into fully mature cells and be enticed into the peripheral circulation; and the other of adult cells which have already obtained entrance into the general circulation, and are temporarily stored in peripheral reservoirs.

The leucocytoses following acute infections and following the experimental exhibitions of sodium nucleinate have been primarily granulocytic in type. It seems legitimate to conclude that nucleic acid, or some of its derivatives, acts definitely as a stimulus to the maturation of the neutrophilic granulocytes. It is well known that there are certain factors which are concerned, at least indirectly, in increasing the numbers of the white blood cells other than the polymorphonuclear neutro-

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philes. For example, Murphy (5) has shown that X-rays and dry heat will increase the number of circulating lymphocytes. Lymphocytes are also markedly elevated in certain diseases, as, for example, pertussis. An increase in the eosinophiles has been observed in certain parasitic diseases and in allergic conditions. Many observers have found that the monocytes are elevated in tuberculosis, in malta fever and in diseases of the liver. It is interesting to note that so far no one has demonstrated that it is possible to produce experimentally the immediate emigration into the peripheral circulation of a large number of white blood cells other than the polymorphonuclear neutrophiles.

The experiments we have to report are interesting in two connections. In the first place, they indicate that there is no store-house for monocytes in the normal organism capable of supplying a great number of these cells on acute demand. In the second place, they indicate that such a store-house is developed in tuberculous animals. These concepts are important both in their relationship to the effect of the tubercle bacillus upon the organism and in demonstrating the limits of flexibility in the supply of monocytes.

The work reported here has been carried on under the direction of Dr. R. S. Cunningham, whose interest, advice and help I wish to acknowledge. Also, I wish to express my appreciation for the advice and assistance generously given by Dr. Edna H. Tompkins.

EXPERIMENTS

In these experiments young healthy guinea pigs were used throughout. They were carefully selected, kept under the same conditions and given the same diet. They were divided into two groups. In the first group all the animals were inoculated with tubercle bacilli and were kept until they began to show some indication of the development of the disease, that is, loss of weight and rise in monocytes. They were then used for the acute experiments, which consisted of the intravenous injections of colon bacilli. The other group was used as controls. That is, they were not inoculated with tubercle bacilli, but were given colon bacilli.

Tubercle bacilli (Strain H37) were grown on Petroff's egg media and were emulsified in the usual manner. The organisms were standardized by the Petroff-Hauser counting chamber so that there were approximately 1,500,000 in each cubic centimetre of the emulsion. Each animal was given 1 cc. of this emulsion intraperitoneally. At autopsy all the

animals inoculated with tubercle bacilli showed involvement of the liver, spleen, peritoneum, omentum and lungs.

The suspensions of colon bacilli were prepared for use in the experiments as follows: Cultures of colon bacilli were grown on agar for 24 hours. They were washed off the agar slants with physiological salt solution and diluted to a suspension of "ground-glass" turbidity. The saline suspensions were prepared for use by refrigerating at about 5°C. for two or more weeks. At the end of this time it was possible to get a weak growth on agar from these suspensions in one of five transplants, so that obviously the majority of the organisms had been killed.

The dose of colon bacilli was determined for the normal animals by injecting from 0.2 to 4.0 cc. of the above suspension intraperitoneally. It was found that less than 0.4 cc. seldom caused a sufficient leucocytosis, and 4.0 cc. sometimes killed the animals, while 3.0 cc. seldom caused death. The range from 0.4 to 1.0 cc. gave an excellent leucocytosis without death. The tuberculous animals were unable to tolerate amounts of the same suspension comparable to those given the normal animals. The quantity of this suspension found effective was from 0.025 to 0.75 cc., according to the weight and condition of the animal, but more than 0.4 cc. sometimes caused death. In the experiments the colon bacilli were injected intravenously in most instances, the leucocytosis being somewhat more marked when the intravenous route was used.

The white blood cell counts were standardized in both groups by the supravital method (1), after which they were ready for the acute experiments. In these experiments the primary interest has been in the leucocytosis produced. The approximate time for the development of leucocytosis, after injection of the colon-bacilli suspension, was determined by making blood counts at two-hour intervals on an initial group of animals. These counts were begun at the time of injection and were continued until they returned to normal. A normal level was usually reëstablished in from thirty-six to seventy-two hours.

The stage of leucopoenia was usually over at the end of 6 hours, and at 12 hours the animals had begun to show a definite leucocytosis. In the series of experiments reported, the suspension of colon bacilli was injected shortly after the last standardizing count, and thereafter counts were made at four- to six-hour intervals, beginning 12 hours after injection.

The control animals were slightly slower in developing a definite

leucocytosis than the tuberculous animals, but this difference was not sufficiently great to be of any significance. Without exception, when an amount of the suspension sufficient to produce a leucocytosis was injected into a tuberculous animal, the animal had a severe reaction, closely resembling an anaphylactic shock. Unfortunately, many of the

TABLE 1

*Control animals**

NUMBER	DOSE	TOTAL WHITE CELLS		POLYMORPHONUCLEAR NEUTROPHILES		MONOCYTES		LYMPHOCYTES	
		Before	After	Before	After	Before	After	Before	After
	cc.								
G-9(A)	1.0	4,480	13,480	2,240	11,862	90	135	2,150	944
G-9(B)	1.0	4,200	13,160	1,722	10,660	84	329	2,394	1,826
G-10	1.0	7,440	17,280	5,134	16,072	300	518	2,232	518
G-13	1.0	11,400	26,280	4,218	23,652	1,368	394	4,332	1,708
G-14	4.0	5,560	12,840	2,502	10,400	500	193	2,530	2,247
G-36	0.5	14,000	50,880	6,702	47,064	1,680	1,272	5,688	1,524
G-63(A)	0.4	17,200	26,280	4,386	21,681	860	788	6,622	3,810
G-63(B)	1.0	24,680	24,800	9,782	21,452	1,110	1,026	10,859	1,644
G-64(A)	0.4	17,240	25,080	8,879	18,058	1,379	2,182	6,724	4,480
G-64(B)	1.0	19,200	28,480	10,752	24,032	1,248	142	6,914	2,986
G-65	1.0	16,800	33,500	9,576	29,986	1,092	1,005	6,132	2,513
G-66(A)	0.4	8,200	15,600	4,182	14,196	369	265	3,362	1,045
G-66(B)	1.0	8,120	22,760	4,750	19,574	447	342	2,842	1,707
G-67(A)	0.4	23,240	23,160	10,225	30,712	1,394	160	8,366	1,124
G-67(B)	1.0	19,640	38,500	9,721	35,035	883	962	6,481	2,502
G-68(A)	0.4	15,360	23,800	4,915	21,896	845	593	5,453	1,309
G-68(B)	1.0	12,240	18,000	4,039	16,470	734	360	5,414	1,170
G-69(A)	0.4	20,560	29,680	12,850	26,919	925	890	5,242	1,899
G-69(B)	1.0	15,800	22,150	9,085	20,488	395	110	5,688	560
G-70(A)	0.4	22,320	30,000	12,271	27,150	492	750	9,151	2,250
G-70(B)	1.0	16,960	26,920	6,020	22,880	1,102	402	7,377	3,634
Average.....	0.92	14,188	24,887	6,855	22,345	824	610	5,522	1,972

* The counts given are the last before the injection of the suspension of colon bacilli and the highest after the injection.

animals died within a few minutes after the injection, and others within from one to five or six hours. The margin between the amount required to produce a leucocytosis of sufficient magnitude, but with the survival of the animal, and the amount which caused immediate death, was found to be very slight. In the control animals this was a negligible factor, as they easily survived amounts five or six times that required to produce

a satisfactory leucocytosis. The tuberculous animals received an average of one-tenth as much as was given to the controls.

In the normal animals, without exception, the leucocytosis produced was entirely in the polymorphonuclear neutrophilic group of cells. The lymphocytes dropped to about one-half of the original number, remained low throughout the experiment and returned to normal slightly later than the other cells. The monocytes maintained a fairly constant level throughout the experiment and showed no change in their character.

TABLE 2

*Tuberculous animals**

NUMBER	DOSE	TOTAL WHITE CELLS		POLYMORPHONUCLEAR NEUTROPHILES		MONOCYTES		LYMPHOCYTES	
		Before	After	Before	After	Before	After	Before	After
	cc.								
G-1	0.250	8,700	26,920	6,541	20,998	1,242	4,501	497	2,019
G-21	0.250	5,440	13,400	3,373	11,256	979	1,608	707	469
G-37	0.100	16,440	29,920	10,933	19,087	2,302	4,916	3,288	6,396
G-38	0.100	25,680	36,680	13,096	29,257	2,698	3,680	9,887	4,158
G-40(A)	0.100	23,480	44,240	15,679	36,719	1,996	5,751	5,987	4,424
G-40(B)	0.250	27,680	55,640	20,989	42,008	2,521	10,016	4,290	3,617
G-43(A)	0.025	13,440	27,000	8,064	22,815	993	1,905	2,688	2,430
G-43(B)	0.050	15,560	26,520	10,425	18,564	1,945	7,076	2,645	3,538
G-43(C)	0.750	22,000	66,440	18,040	55,810	1,100	7,441	2,530	3,709
G-54	0.050	17,240	51,440	11,465	43,724	2,672	6,687	3,103	823
G-55	0.050	22,400	43,840	17,584	36,326	1,792	6,561	2,352	3,288
G-57(A)	0.050	24,040	43,400	16,588	36,673	2,644	3,255	5,468	3,472
G-57(B)	0.100	23,000	62,520	16,675	49,702	3,795	9,197	2,415	4,064
G-58	0.100	17,600	52,880	10,880	43,362	2,288	9,132	3,608	2,380
G-60	0.100	13,600	35,280	9,384	29,635	1,760	3,923	2,176	2,293
Average....	0.092	18,420	41,008	12,648	33,062	2,049	5,710	3,443	3,129

* The counts given are the last before the injection of the suspension of colon bacilli and the highest after the injection.

In the tuberculous animals the picture presented was strikingly different. There was indeed a polymorphonuclear leucocytosis, but this did not follow the curve of the total white blood cells as closely as in the nontuberculous animals. The lymphocytes dropped slightly, remained at a constant level, or rose slightly. At the time of the maximum polymorphonuclear rise, the lymphocytes had dropped in approximately one-half of the experiments, the other half showing a rise. The average of the change at this time showed a fairly constant level. At some time

during each experiment on a tuberculous animal, the lymphocytes dropped to about one-half their original level. The curve of the lymphocytes was always the first to return to its original level.

A definite rise in monocytes occurred in every tuberculous animal studied; in most of them this rise essentially paralleled the rise in the

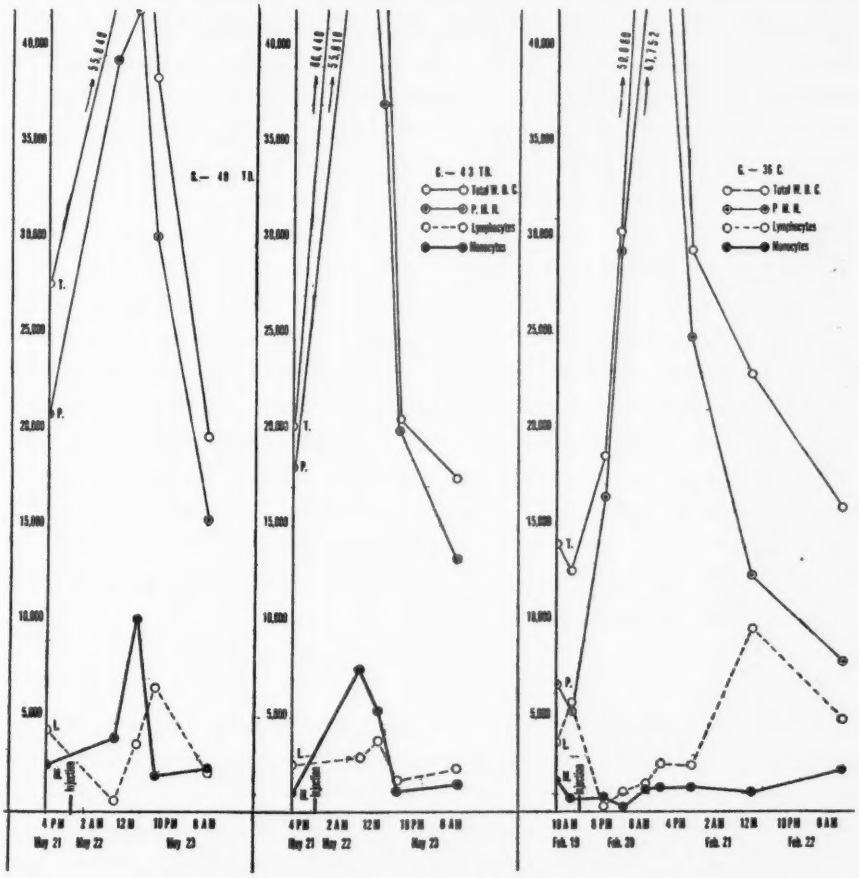

CHART 1. Illustrates the counts obtained in two tuberculous animals and in one control animal. The counts are recorded in absolute number per cubic millimetre of blood.

total white blood cells and the polymorphonuclear leucocytes, a condition never found in the control animals. There was also a striking change in the character of the monocytes in the circulating blood. The monocytes in tuberculous animals, before they were injected with the suspension of colon bacilli, were typically tuberculous in character.

After the injection of colon bacilli, there was a marked increase in the number of monocytes which were epithelioid in character. In these cells the rosette tended to disappear as a result of the accumulation of more and more fine neutral-red vacuoles. Many of these cells also contained numerous fat droplets in the peripheral part of the cytoplasm. It was noted in a few of the acute experiments that some of the epithelioid cells contained bacilli. None of the bacilli were surrounded by digestion vacuoles. It is well known that epithelioid cells containing tubercle bacilli are to be found in profusion in foci of infection with the tubercle bacilli; in fact, they are a characteristic part of the tuberculous lesion. As the leucocytosis approached its peak, the number of monocytes of the epithelioid type in the smears increased, and, strikingly, the number of such cells containing bacilli also increased. No cells resembling epithelioid cells were observed in the smears from the normal animals. As the leucocytosis passed its peak, which usually occurred about eighteen hours after the injection of the bacillary suspension, and the curves returned to normal, the epithelioid cells containing bacilli disappeared. Later, all typical epithelioid cells disappeared entirely, and, by the time the number of the white blood cells reached the original level, all the monocytes were of the type usually found in tuberculous animals. In this series of experiments, the monocytes in the tuberculous animals have been found to increase from an initial level of 1,000 or 2,000 per cubic millimetre of blood to as high as 10,000 within a period of fifteen to eighteen hours.

CONCLUSIONS

1. There is, in the normal nontuberculous animal, no reservoir or store-house for monocytes capable of supplying great numbers of these cells upon acute demand.

2. Such a reservoir can be and is established in tuberculous animals.

3. After the establishment of such a store-house for monocytes, they respond to acute stimuli in a manner similar to that shown by the granulocytic leucocytes.

4. There is a possible clinical application in this work. The number and character of the monocytes should be very carefully examined in all cases in which it is possible that an acute pyogenic infection is masking a tuberculous process.

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OBSERVATIONS ON PERSONS WITH POTENTIAL VITAMIN DEFICIENCY[1,2]

BURGESS GORDON AND ELIZABETH FLANDERS

The striking results noted in the experimental studies of vitamins have aroused considerable discussion as to possibilities for clinical application. Although important data have been obtained, the question has been raised as to interpretation of the parallel drawn between vitamin deficiency in man and that induced artificially in animals. However this may be considered, the results in the treatment of rickets, beri beri and scurvy (1) leave no doubt as to the effects of vitamins. It appears that, if criticism exists, it is due not to the failure to recognize the importance of accessory food substances but rather the tendency to emphasize the spectacular, and disregard, to some extent, the danger of overdosage and the value of intelligent dietetic measures.

It has been suggested that the endocrine glands, the mobilization and utilization of mineral salts, and heliotherapy are factors in tissue repair. The question of calcium metabolism in tuberculosis was studied at the Chest Department of the Jefferson Hospital, to note the effects of parathyroid hormone, heliotherapy and calcium lactate on calcification of pulmonary lesions (2). Although decreased cough and expectoration, cessation of haemorrhage, increased strength and a sensation of well-being occurred in certain instances, there was no evidence to suggest that hypercalcaemia influenced specifically the deposition of lime salts in the lungs. It appeared in the more recent observations that the clinical manifestations were less constant when a reduction in the caloric intake occurred. In a study of workers who had been associated with the Department from a few weeks to fifteen years it was found that the incidence of tuberculosis was less than 2 per cent (3). The high caloric

[1] From the Medical Service of Dr. Thomas McCrae and the Department for Diseases of the Chest, Jefferson Hospital, Philadelphia, Pennsylvania. A part of the expense of this investigation was defrayed by grants from the Lessing J. Rosenwald Fund and the Anne Woodhull White Fund.

[2] Read at the annual meeting of the Association of American Physicians, Atlantic City, New Jersey, May 6, 1930.

diet, rich in foods prepared from starch and dairy products, was suggested as a possible factor in the prevention of disease.

In view of these observations and the apparent relationship between certain vitamins and mineral metabolism, the following study was undertaken: In 1185 new patients entering the clinic from February 15, 1929, to April 1, 1930, a careful study of the food intake with special reference to accessory food substances was made. In addition, a search was undertaken to determine phenomena suggesting lack of vitamins. This group included white and colored patients, tuberculous (approximately 40 per cent) and nontuberculous (approximately 60 per cent), varying in age from three to fifty-six years. Approximately 35 per cent were children (57 were less than 12 years of age), the majority of whom were so called "contact" patients. The physical examinations included roentgenograms of the chest and in certain instances of the arms and legs, with determinations of the amounts of calcium and phosphorus in the blood.

The figures showed that the average food consumption was low, perhaps less than 1400 calories. It was not uncommon to find adult patients who lived on an intake of from 800–1000 calories daily. In most instances the intake was derived from meat, potatoes, bread and canned vegetables. The use of cereals, green vegetables and fruit was distinctly variable. A striking feature of the dietaries studied was the low consumption of milk and butter. Although this was due largely to economic reasons, it was evident that, as the appetite failed or the disease progressed, there was a sharp decline in the use of dairy products.

As regards the different classes of patients studied, it was found in those with far-advanced tuberculosis (380) that it was impossible to differentiate between manifestations resulting from disease and those due to the insufficient intake of food or accessory food substances. It was obvious, however, in many patients with incipient or moderately advanced tuberculous disease (approximately 200), that symptoms such as weakness, nervousness and insomnia could be explained in part by insufficient food. A second group, composed of (about 300) nontuberculous patients, complained of fatigue, loss of appetite, intercurrent infections and not infrequently restlessness and insomnia. In the majority of instances the study suggested that symptoms were due chiefly to unsuitable food intake. It was evident that mistaken ideas as to special diets were not uncommon. A third group, comprised of about 400 so called "contact" patients (nontuberculous), had no symp-

toms and were interested primarily in advice about prevention of disease.

In the physical examinations, apart from evidence of pulmonary tuberculosis, undernutrition and a few special medical conditions there were no striking variations from normal; of special interest, perhaps, was the comparatively rare outstanding evidence of rickets. The findings in the roentgenographic studies were in agreement with the clinical observations. The blood calcium and phosphorus determinations were within normal limits.

A special class of 46 tuberculous and 110 nontuberculous patients (with symptoms) was formed from the three general groups to determine the effects of supplementary vitamin A and D administration.[3] A further series of 14 ward patients (tuberculous) were observed, to note the influence of mineral concentrate[4] and butter. In these patients no changes were made in the customary intake of food and, except for cathartics, sedatives and in certain instances occasional administration of parathyroid hormone (Lilly), for pulmonary haemorrhage, no drugs were permitted during the study.

The tabulations in the studies of codliver-oil concentrate showed that 31 patients (10 tuberculous and 21 nontuberculous) gained from 2 to 5 kg. and five patients (3 tuberculous) showed a gain up to 10 kg. There were 14 children in this group, in whom growth was apparently a factor in the increase of body weight. A decrease in intercurrent infections, as compared to previous years, was noted in approximately 35 per cent of patients receiving the concentrate, and a further comparison made with individuals in the general group suggested also a lower incidence of infections: as, for example, two children, living in a street occupied by 14 families with 34 children, were essentially free from tonsillitis rhinitis and laryngitis, whereas respiratory infections were not infrequent in the neighborhood. In this instance figures on the caloric intake were not obtained except in the two children under observation, who, incidentally, lived on a well-cooked dietary of approximately 2000 calories daily. A sensation of well-being and increased appetite was

[3] Vitamins A and D were supplied in the form of tablets, prepared from codliver oil and flavored with anise, orange and vanilla and cassia. The dosage varied from 3 to 10 tablets daily, equivalent approximately in vitamin content to 0.5–2.5 teaspoonfuls of codliver oil.

[4] The mineral concentrate mixture contained 77 per cent anhydrous whey, 19 per cent sucrose and 4 per cent cocoa, and the dosage was 100 gm. dissolved in 100 cc. of water and served with 10 gm. of butter (to provide approximately the same amount of fat and vitamin A as when milk is taken) at 10 A.M. and 8:30 P.M.

noted in 35 per cent of the patients. These manifestations were present usually when gain in weight and decrease in upper respiratory infections occurred. It was evident that response to administration was more definite in patients who consumed liberal portions of cereals, dairy products and green vegetables.

In the physical examinations and roentgen-ray studies there was no evidence of fibrosis or deposition of lime salts in the lungs that could not be attributed to the ordinary process of healing; significant change in the bones of the arms or legs and visualization of vessels was not observed. The blood-calcium and phosphorus levels were variable and showed no apparent relationship to the dosage of codliver oil concentrate.

In patients who consumed mineral concentrate (whey) and butter there was likewise no objective evidence that pulmonary lesions were influenced specifically. A gain in weight of from 2 to 5 kg., decreased cough and expectoration, and a sensation of well-being occurred in 10 of the 14 patients observed during a period of two months.

Obviously it is difficult to appraise the effects of dietetic measures in pulmonary tuberculosis because the course of the disease is characterized by variations in activity. In so called "contact" patients, apart from the effects of a smouldering process, sociological features may influence the physical condition. It is true also that estimates of the food intake may be subject to error because of inaccurate histories given by certain patients. It appears, however, that the trend in all patients coming to the clinic is toward a low caloric intake and in many patients a striking reduction in the consumption of dairy products. The signs and symptoms do not suggest vitamin-D deficiency. It would appear that the source of this vitamin is ample for requirements; at least, the administration of vitamin concentrate failed to cause striking effects. The results noted following the supplementary feeding of whey (vitamin-free) suggest that concentrated mineral salts should be considered in the diet of patients unable to tolerate or afford a satisfactory intake of milk. Apart from any specific influence, minerals may be considered as necessary substances for effective vitamin action. Considered speculatively, it is possible that a close relationship exists between minerals, calories, vitamins, and substances such as carotin. This may account for the effects of codliver oil which has been used empirically for many years.

The comparative frequency of upper respiratory infections may be explained on the basis of home surroundings rather than the dietary followed, but it is interesting to note that the incidence decreased fol-

lowing the administration of codliver-oil concentrate. This may be significant in view of the observations of Wolbach and Howe (4), who found changes in the epithelium of the respiratory tract following the withdrawal of vitamin A. It is generally considered that vitamin A influences the appetite; if so, this would increase the consumption of food, and, apart from any specific change in the tissues, would result in a gain in weight and sensation of well-being. The study appears to parallel the work of Kramer, Grayzel and Shear (5), who found no striking change following the administration of *viosterol* in tuberculous children and the observations of McConkey (6) and Smith (7) on the effects of codliver oil and tomato juice, and the more recent studies of Mayer and Kugelmass (8). It appears that codliver-oil concentrate may be administered with value, but the effectiveness depends largely on vitamin-A fraction, a well-balanced diet, the supply of calories, mineral constituents, and perhaps other undetermined food factors.

CONCLUSIONS

1. It appears that the caloric intake of clinic patients between 12 and 56 years of age is a more serious problem than the question of potential vitamin deficiency.

2. The average caloric intake was approximately 1400, but numerous individuals were found who lived on 800–1000 calories daily, and not infrequently the dietaries were extremely low in cereals, green vegetables and dairy products.

3. Although vitamin-D deficiency may have occurred in early childhood, striking evidence suggesting continuance or untoward effect in recent years could not be established.

4. The frequency of intercurrent infections and other phenomena suggested a deficiency in the intake of vitamin A.

5. The administration of codliver-oil concentrate failed to influence the deposition of lime salts in diseased pulmonary tissue. This suggested that supplementary vitamin-D administration was either unnecessary because a sufficient intake was derived from various natural sources or because a specific effect does not occur in the mechanisms studied.

6. The effects of codliver-oil concentrate on various respiratory symptoms suggested that supplementary vitamin-A administration is of distinct value.

7. The apparent influence of mineral concentrate suggests that various substances derived from a natural source (milk) may be of value in the management of infection and malnutrition. If comparison is justified it appears that the effects are more definite than those attributed to the supplementary feeding of vitamin D.

We are indebted to Drs. John T. Farrell, Jr., En Shui Tai and Miss Sara Morton for valuable assistance in this study.

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THE INTRAMUSCULAR USE OF SODIUM AMYTAL IN ADVANCED TUBERCULOSIS

HOMER H. CHERRY[1]

Realizing that it is very often necessary to resort to the use of analgesics and hypnotics when terminal-stage tuberculosis is being treated, the following observations on the use of sodium amytal as a hypnotic and analgesic are presented. It is felt that a drug having fewer side actions than the opium derivatives, such as habit-formation, delay of gastrointestinal motility and immediate elevation of tolerance, has been needed. So far it seems very likely that sodium amytal may supply this need. Intramuscular administration seems to be the preferred way.

Case Reports

S. Z., white female, age 25 years, terminal-stage tuberculosis, larynx and gastrointestinal tract clinically negative. Cough persistent and constant, and worse at night, resulting in insomnia. Four grains of sodium amytal, given intramuscularly in the early evening produced restful sleep and marked alleviation of cough during the night, and during the forenoon following the patient was restful. No headache or local discomfort produced; no excitation; blood-pressure not disturbed.

R. V., white female, age 25, terminal-stage tuberculosis, larynx and gastrointestinal tract clinically negative. Cough persistent and constant. Patient had vomited for 48 hours intermittently large amounts of green liquid, apparently indicative of adynamic gastric ileus. All treatment had been of no avail. Five grains of sodium amytal given into the muscle accompanied by 200 cc. of physiological saline solution in the vein. Patient ceased vomiting, cough improved, eight hours of restful sleep was secured, and the ten hours following this sleep were restful. The patient was said to have had mild excitation during sleep which she did not recall on awakening. No headache, and blood-pressure not disturbed.

E. M., white male, age 30 years, terminal-stage tuberculosis. Patient had marked abdominal cramps due to severe tuberculous enterocolitis. Three

[1] Louisville, Kentucky.

grains of sodium amytal produced a restful night, free from abdominal pain; no headache, excitation or local discomfort; blood-pressure not disturbed.

A. B., white male, age 55. Recto-sigmoid faecal impaction. Marked internal haemorrhoids, producing excruciating pain and tenesmus. Two hundred cubic centimetres of mineral oil given as a high retention enema with a urethral catheter. Five grains of sodium amytal intramuscularly followed this. Tenesmus, straining and insomnia all relieved for ten hours. Oil was retained. Patient was observed to be excited and talkative during sleep, getting out of bed. He knew nothing of this, however, on awakening. No headache or local discomfort; blood-pressure not disturbed.

V. D., white female, age 22, a very nervous and erratic individual. She could not be encouraged to submit to dental extraction. Three and a half grains of sodium amytal given intramuscularly produced cessation of apprehension, and patient seemed not disturbed at submitting to extraction 2½ hours later. No headache, local discomfort or blood-pressure change.

Six girls and two boys ranging from 8 to 14 years of age. Three grains of sodium amytal given intramuscularly produced marked alleviation of apprehension and nervousness when attempting pulmonary lipiodol injections. There was marked contrast to an attempt at the same procedure without the sodium amytal. Pharyngeal reflexes seemed markedly restrained. No change in blood-pressure, local discomfort or headache was noted. No excitation. Five per cent butyn sol··tion was also used.

C. L., female, age 38. Acute ischiorectal abscess had been incised, following which patient had marked pain. Four grains of sodium amytal gave ample relief from pain for ten hours. No excitement, alteration of blood-pressure or headache occurred.

S. T., white female, age 25. Four grains of sodium amytal given intramuscularly followed by pulmonary lipiodol injection two hours later. Marked alleviation of pharyngeal reflexes, general nervousness and apprehension. Five per cent butyn was used as a pharyngeal and laryngeal spray. Our system consists in introducing the oil directly into the trachea with a cannula inserted between the cords. The sodium amytal undoubtedly augmented the butyn effect. No untoward effects.

E. S., white male, age 25, terminal-stage tuberculosis. Painful tuberculous larynx. Cough very irritating. No sleep at night due to cough and laryngeal pain. Five grains of sodium amytal intramuscularly gave complete rest and

sleep. Pain and cough abolished for 9 hours. The morning following was restful. No untoward effects. Blood-pressure not disturbed.

SUMMARY

Sodium-iso-amyl-ethyl-barbiturate crystallizes in fairly dilute solutions on standing exposed to the atmosphere. When injected intramuscularly it produces no local pain or tissue change even in the most emaciated persons. Physiologically, however, within fifteen minutes after injection in therapeutic doses the patients begin to experience mild cerebral depression, so that apprehension and muscular tension seem markedly restrained. The thalamus, along with the medulla, seems to be markedly influenced so that (1) pain and sensory reflexes are restrained. These actions of the drug grow in intensity for a period of three to four hours and are prolonged over a period of eight to twenty-four hours, according to the size of the dose. In no instance have I seen complete narcosis approached when the dose did not exceed eight grains. Similar amounts do not produce sleep from which the patient cannot be easily and quickly awakened to clear consciousness. Occasionally sleep is not without excitation, causing the patient to talk and move about in bed. The blood-pressure or respiratory cycle is not appreciably disturbed as was observed by Link (2) and others.

Gastrointestinal motility is not disturbed, although almost every case presenting abdominal pain experienced marked alleviation. This would coincide with observations made on uterine contractions by other workers (1), who found motility not to be disturbed although the pain was abolished.

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(2) Experiments by Link of Indianapolis, Indiana.

THE MEASUREMENT OF A GENERALIZED NURSING SERVICE IN TWO SOUTHERN CITIES IN RELATION TO TUBERCULOSIS CONTROL[1]

ERNEST T. KRUEGER[2]

This paper deals with the community aspects of the tuberculosis nursing service of the cities of Nashville, Tennessee, and Birmingham, Alabama. I have taken "community aspects" to mean the interrelation and coördination of the nursing service with welfare organizations whose work is sufficiently significant in tuberculosis control to affect vitally the efficiency of the nursing service. Statistics and descriptive information were therefore gathered for the following types of welfare work:

1: School hygiene, including medical examinations, school nursing and open-air rooms
2: Sanatoria, including hospitals, preventoria and fresh-air camps
3: Education
4: Family welfare, including family relief work, medical social work, and vocational readjustment work

This paper, therefore, will briefly describe (1) the chief agencies and institutions of each of the two cities which render tuberculosis service, (2) the coördination and integration of the tuberculosis work of these agencies with the nursing service and with each other, and (3) the strengths and weaknesses which appear in the general situation. No attempt will be made to evaluate quantitatively, by scoring devices, the tuberculosis services of these agencies and institutions, but rather to present a picture of the situation as a whole.

SCHOOL HYGIENE

Nashville's public-school hygiene is under the direction of the school authorities. The program calls for a general medical examination of all grade-school children every two years, a yearly examination of all school

[1] Read at a session of the Sociological Section at the twenty-sixth annual meeting of the National Tuberculosis Association, Memphis, Tennessee, May 9, 1930.

[2] Vanderbilt University, Nashville, Tennessee.

teachers (a legal requirement) and the examination of boys seeking admission to the R. O. T. C. During periods of threatened epidemics of typhoid fever or diphtheria, the medical staff has entered upon extensive campaigns of inoculation of children against these diseases.

The staff consists of two part-time physicians, one white and one colored, one part-time dentist, and three full-time nurses, two white and one colored, for some 23,000 school children. The medical examination of school children in this city is routine and rapid, about 35 children being examined per hour. Underweight children are given some special dietary attention in the schools they attend, especially if they come from homes in poor circumstances. The work of the school nurses is practically confined to assisting the physicians, keeping records and sending notices to parents.

Health education is largely limited to school-room and textbook instruction, and is otherwise dependent upon the interest and initiative of school principals and teachers. There is no supervisor of health education and no special program of nutrition classes.

The parochial and private schools and children's institutions were not included in this study.

From the standpoint of community control of tuberculosis, the present plan of medical examination of all public-school children every two years calls for a much larger medical staff and a more effective coördination with community agencies, if the work is to be efficient. In 1928 five tuberculosis suspects were found. These were referred to private physicians or to clinics and a certificate required before readmittance to school. The public-school program as a whole does not seem to lend itself to an effective means of health instruction or follow-up of underweight children, and is hence greatly limited in its possibilities for preventive tuberculosis work. The public schools do not possess open-air school-rooms and make no special effort along this line. The interrelation of the school medical work with the nursing service is a negligible one.

The city Health Department, however, supplements the school program through mass tuberculin testing in the schools. In positive cases, parents are urged to take the child to a physician and requested to furnish the name of the family physician and to give a family history of the disease. The Health Department reports a 90 per cent return on these requests. Physicians are then supplied by letter with the names of children of clients who show positive reactions. This general attack on

tuberculosis in the community has an obvious educational as well as medical value. The Health Department is also, at present, engaged in an extensive experiment on school and institutional children with Calmette's *BCG* vaccine.

Birmingham has an extensive school-hygiene program. Medical examination of school children is under the direction of a Child Health Department employing three part-time physicians, two white and one colored, and one part-time white dentist. The program calls for examination of all first-, fifth- and eighth-grade children. Medical examination is coördinated with a program of health instruction and follow-up work. The latter, however, is carried on under the direction of the Jefferson County Anti-Tuberculosis Association. The School Board furnishes one white and one colored health teacher and the Anti-Tuberculosis Association supplies three white and one colored health teachers, a total of four white and two colored workers. The program includes the parochial schools, although the work is more limited in scope. Some idea of the extensiveness of this general health program may be gained by the following figures for public and parochial schools, white and colored, for the year 1928–1929.

Schools having organized nutrition classes	20
Classes organized	115
Pupils enrolled	3,166
Classes conducted	2,820
House visits	1,259
General health talks in schools	893
School children brought to throat clinics	23
School children brought to eye clinics	53
School children brought to dental clinics	114
School children brought to tuberculosis clinics	266

From the standpoint of tuberculosis education and control, the school-hygiene program of Birmingham presents an attractive picture of preventive work. The fact that the Anti-Tuberculosis Association also maintains a well-equipped chest clinic and correlates the work of medical examinations and health instruction with the clinic promotes the work of prevention and diagnosis of tuberculosis among school children. Co-operation with the Health Department consists in notification of the nursing service of all active cases of tuberculous school children.

SANATORIA

Hospitalization of the tuberculous in both cities is largely confined to facilities provided by county sanatoria, although the Davidson County Anti-Tuberculosis Association has been maintaining a small preventorium for suspects and undernourished children. Nashville has a summer fresh-air camp for white children and Birmingham has a camp for both white and colored.

The Davidson County Tuberculosis Hospital at Nashville provides 180 beds for white adults, 30 beds for colored adults and 30 beds for white children. The waiting list as of April 3, 1930, was whites 68, colored 27. On the basis of 2,000 patient days per 100 deaths, the Davidson County hospital is short some 11,000 patient days. The deficiency is probably related to the colored population rather than to the white. The problem of hospitalization of the colored is a triple one: (1) the need of more beds, (2) the high death-rate among colored patients, and (3) the difficulty of getting negroes to enter the hospital until the disease has reached an acute stage. The waiting-list figures, which are typical, indicate a need for more beds for both races and the fact undoubtedly affects the efficiency and control aspects of the nursing service in the community.

The preventorium of the hospital is exceptionally well housed and operated from a medical and social point of view. The city School Board provides a teacher for the children and ample play facilities are at hand for the less advanced cases.

Integration with the nursing service occurs through hospitalization and through the Tuesday chest clinic for whites and the Saturday chest clinic for colored to which the nursing service sends suspects, the Health Department furnishing transportation. Integration with the nursing service is further obtained through notification of discharged patients and renotification if patients fail to return for the required two months' and six months' reëxaminations. Contact for a two-year period is attempted by the hospital.

The hospital maintains a social worker, who is also a nurse, who looks into the economic status of prospective patients, but who indirectly aids in home education and in the encouragement of persons to seek hospitalization.

The superintendent of the institution advises all discharged patients regarding vocational readjustment and, because of his long acquaintance

with employers in the city, does a great deal of reëmployment and placement work. No record is made, however, of the vocational instructions given.

The gaps in the integrative aspects of the hospital service with the nursing service and with other community services are those of home preparation for the return of the patient and a social follow-up of the patient after discharge with reference to vocational and economic problems.

The Jefferson County Tuberculosis Sanitarium at Birmingham has 52 beds for white adults, 20 beds for negro adults and 16 beds for white children. The waiting list is from 12 to 15 adult whites, 20 to 25 adult negroes, and 7 to 10 white children. The preventorium is well housed and managed and has facilities for school work and play.

Considering the fact that Birmingham is more than half again as large as Nashville, the tuberculosis hospitalization program of the city seems deficient. The small waiting list seems to indicate, further, that the forces of the city are not adequately organized to make the most use of its sanatorium or to encourage its enlargement. It is recognized, of course, that waiting lists are not always a safe criterion, since patients fail to materialize when vacancies occur, and this is especially true of the colored race.

The hospital notifies the nursing division of the Board of Health concerning all discharged patients and sends a duplicate to the chest clinic maintained by the Anti-Tuberculosis Society. Patients are urged to return every two months for reëxamination. The superintendent advises all discharged patients concerning vocational readjustment, and, where possible, arranges with previous employers for the return of the patient to work. Vocational advice, happily, is written into the patient's record. The hospital officials feel, as do officials of other services in the community, that the follow-up work is deficient and the integrative program defective. The situation is now being studied, locally, relative to a more adequate coördination and integration of services touching (1) home preparation for the return of hospitalized persons, (2) the furnishing of appraisals of work capacity to follow-up agencies, (3) reemployment and vocational training, and (4) follow-up services in general on the part of nurses, clinicians and social workers.

ANTITUBERCULOSIS ASSOCIATIONS

Antituberculosis associations, usually, are presumed to undertake educational programs, to coöperate with existing local agencies dealing

with tuberculosis, and to initiate new programs which eventually may be turned over to local health agencies.

The Davidson County Anti-Tuberculosis Association of Nashville contributes to the tuberculosis educational program of the city through the distribution of health literature, posters, stickers and bill-board displays.

The Association also participates in local relief work by providing milk, food, clothing, coal, rents, sleeping porches, and, in some instances, servants in homes of tuberculous mothers. Cases are cleared with the nursing service and the Charities Commission to prevent overlapping with the latter organization.

Perhaps the best work of this organization, other than its educational work, lies in the tendency in recent years to use a part of its funds to bolster needs of existing local health agencies. At the present time the Association gives a thousand dollars toward the Hubbard chest clinic for the colored. It also provided, this past year, three public-health nursing scholarships at Peabody College, and appropriated money toward a survey of the entire health set-up in the city.

The Jefferson County Anti-Tuberculosis Association of Birmingham, with a budget of about $14,000, confines its program to the maintenance of a chest and throat clinic, through which much of the tuberculosis clinical work of the city is carried on, and to the operation of an extensive plan of nutrition and educational work for public-school children. It does not maintain sanatoria of any sort and seems not to participate in family-relief work. Its work for the public school children takes its workers into the homes of school children and links the nutrition work with its clinic and the County Sanatorium.

The integration of the Association's work with existing nursing, hospital and social-welfare agencies and institutions takes the following form: Clinical cases are reported to the nursing division of the Health Department, and all positive cases are reported to the Bureau of Vital Statistics. All clinical cases are cleared through the Confidential Exchange. In turn, the nursing service utilizes the clinics for diagnostic work as does the Red Cross Family Service.

The general hook-up, however, of the work of the Association, the Sanatorium, the Health Department, nursing service and the family welfare agencies does not seem to work as efficiently as it might. There is a serious gap in the follow-up work of patients discharged from the sanatorium, and there is some tendency toward individualization and

isolation of functions in the integrative aspect of the set-up of tuberculosis work.

EDUCATION

We have made no comprehensive study of tuberculosis education, in the two cities, except that of the schools and the antituberculosis associations. The health departments also do a great deal by way of direct instruction in families and by the distribution of literature. It is my opinion that a more adequate extension of family case-work in coöperation with nursing service would promote the educational aspects of tuberculosis control.

FAMILY-WELFARE AGENCIES

The work of family-welfare agencies everywhere seems to be moving in the direction of family rehabilitation and readjustment rather than in the direction of purely relief functions. The sociological approach to family life recognizes that economic family problems are closely related to communal and cultural processes on the one hand, and to individual processes involving physical and mental health, general training and personality traits on the other hand. This shift in conception of family social work has had important implications. It has demanded expert knowledge of family life on the part of family social workers, a familiarity with the interactional processes which go on within the family and the community. I am injecting this statement of point of view, because tuberculosis is essentially a family disease and its treatment in its present stage calls for expert dove-tailing between the medical and the social aspects of control. Paralleling the work of the physician and the nurse must come that of the social worker trained to solve peculiarities of family organization and the vocational and economic problems which are forever arising not only in the less competent portion of the population, but wherever a disease like tuberculosis strikes the heart of family and individual life, placing a serious tax on resources, endangering the entire family through cross-infection, and often demanding a grave readjustment in habits and attitudes and in the mode of earning a living or bearing one's share of labor.

Because of the importance of family-welfare work, we were interested in getting a cross-section of the participation of the family agencies of Nashville and Birmingham in tuberculosis control in their respective cities. All the family cases for a year were taken which showed the

presence of tuberculosis in the family. A mimeographed schedule was prepared, calculated to secure on each case the following information:

1: The composition of the family and the age and tuberculosis history of its members
2: The social problems which the presence of tuberculosis has introduced or accentuated
3: How the case came to the attention of the agency
4: How the presence of tuberculosis was discovered and by whom or through what agency
5: The previous agencies dealing with the family and for what purpose
6: Whether conferences with other agencies took place and the results of such conferences
7: The program of treatment of family problems initiated by the family agency
8: What favorable results were secured
9: What part of the program failed and the unfavorable conditions preventing its entire success

I propose now to describe briefly the work of the Davidson County Charities Commission of Nashville and the Red Cross Family Service of Birmingham and then to summarize the results of the cross-section study. Both of these agencies have the same number of field workers, seven white and one colored, each has one supervisor, and both have a yearly budget of approximately $40,000. We did not attempt a study of the work of the Jewish Charities, the Salvation Army or similar organizations, which do some family work.

Coöperation and integration in both cities between the family-welfare agency and the nursing service of the Health Department have been developed. Families of tuberculosis patients needing relief are referred by the nursing service to the family-welfare agencies, and families in which tuberculosis is discovered are referred by the welfare agencies to the nursing service. Through conference, services are coördinated and worked out.

The Nashville situation presents some complications which must be noted. Tuberculosis cases needing family social work or relief are referred to the Charities Commission if the family is or has been a client of the Commission. New cases are referred to the antituberculosis association. This division of labor is probably the result of the willingness of the antituberculosis association to put money into relief and to undertake such matters as building sleeping porches, carrying rents,

The complete data of the cross-sectional findings are as follows:

	NASHVILLE		BIRMINGHAM	
	Total number	Per cent	Total number	Per cent
Total number of families	27	100	77	100.0
Fathers having tuberculosis	11	40.7	35	45.3
Mothers having tuberculosis	12	44.4	32	41.5
Families having children	26	96.0	66	85.7
Total number of children	85	3.1	190	2.8
Active	9	10.6	15	7.9
Incipient	1		1	
Suspects	8	9.4	1	
Arrested	0		2	
Total tuberculosis	18	20.1	19	10.0
Fathers dead, deserted, divorced	7	25.9	20	26.0
Mothers dead, deserted, divorced	2	7.4	2	
Family problems				
Economic	19	70.1	63	81.8
Employment	10	37.0	38	49.3
Sanitation	9	33.3	24	31.2
Diet	12	44.4	49	63.6
Space	3	11.1	24	31.3
Care of patient	5	18.5	18	23.4
Contact situation	9	33.3	30	38.9
How cases originated				
Application for relief	6	22.0	26	33.7
Request of physician	8	29.6	18	23.4
Request other agencies	12	44.4	33	42.8
Discovery of disease				
Known to family	5	18.5	28	36.3
Other agencies	17	62.9	24	31.2
Private physician	1		5	6.5
F. W. A.	4	14.8	20	25.9
Agencies in contact previous to F. W. A.				
Nursing service (H. D.)	13	48.1	30	38.9
Medical hospital clinic	7	25.9		
Church	1		2	
Antituberculosis association	6	22.2	25	32.4 (clinic)
Agencies coöperating with F. W. A.				
Nursing service	9	33.3	39	50.6
Medical hospital clinic	9	33.3		
Antituberculosis association	5	18.5	16	20.8 (clinic)
Others (one or more)	2	7.4	18	23.2
Number on which conferences were held	10	37.0	47	61.0
Program of treatment				
Relief	19	70.3	40	51.9
Supplementary diet	4	14.8	21	27.2
Medical examination	5	18.5	21	27.2
Employment adjustment	4	14.8	5	6.5
Hospitalization	7	25.9	33	42.8

	NASHVILLE		BIRMINGHAM	
	Total number	Per cent	Total number	Per cent
Program of treatment				
Waiting list	3	11.1	9	11.9
Special nursing	1		2	
Locating relatives	1		3	
Unfavorable conditions				
Lack of coöperation	4	14.8	9	11.6
Shiftlessness of father	2	7.4	1	
Shiftlessness of mother	1			
Refusal of hospitalization	4	14.8	12	15.6
Refusal to stay in hospital	2	7.4	10	12.9
Death of patient	7	25.9	17	22.0
Removal from city			7	9.1
Mental problem	1		3	3.9

supplying milk and clothing, or providing house help to tuberculous mothers. Thus duplication has been prevented, but the situation complicated by a division of responsibility for family social work.

The Nashville situation is further complicated by the fact that Vanderbilt University, with an adult chest clinic meeting three times a week and a general pediatrics clinic, maintains a well-organized department of medical social work. In 1929 this department had 102 tuberculosis cases referred to it, 97 of which were contacted and visited. Close cooperation between the Vanderbilt medical social work and the work of the health-department nursing service, the family-welfare agency and the antituberculosis association is, however, maintained. Relief assistance is secured from the family-welfare agency. The excellent quality of the medical social work is an asset to the city.

At the present time the family-welfare agency in Nashville through a local committee is studying its responsibility in tuberculosis control. It is seeking to discover the extent of the problem, the number of tuberculous families needing relief and social service, and the agencies which now give social service. It hopes to perfect a satisfactory approach to the whole problem.

The cross-sectional study of the tuberculosis cases carried by the family welfare agencies of the two cities has revealed some very interesting results. The Davidson County Charities Commission of Nashville in 1929 did case-work on 27 tuberculous families, 17 white and

10 colored, or 1.9 per cent of a total family case-load of 1,411. It will be recalled, however, that in Nashville the antituberculosis association and Vanderbilt Hospital do case-work on tuberculous families. The Red Cross Family Service of Birmingham did case-work on 77 tuberculous families, 43 white and 20 colored (14 being undesignated as to race), or 3.9 per cent of a total family load of 1,992. Percentages of total case-loads for both cities seem very small.

The analysis of the above table reveals certain interesting facts: for instance, 40.7 per cent of Nashville family-welfare tuberculosis cases show fathers having the disease and 44.4 per cent of the mothers; in Birmingham 45.3 per cent of the fathers, and 45.5 per cent of the mothers.

In Nashville 96 per cent of the families had children, 85 in all, or an average of 3.1 children for all families, while 20.1 per cent of the children showed tuberculosis in some form. In Birmingham 85.7 per cent of the families had children, 190 in all, or an average of 2.8 for all families; 10 per cent showed tuberculosis in some form. Records of children having the disease, however, are probably not complete for either agency. In Nashville 25.9 per cent of the fathers are dead, deserted, or divorced; in Birmingham, 26 per cent.

The family problems, as might be expected, ran high on economic, diet and contact situations. Of immediate interest to this paper is the integration of agency services. In both cities more than 40 per cent of the cases originated through reference by other agencies. In Nashville 14.8 per cent of the cases owe the discovery of the disease to the family-welfare agency; in Birmingham, 25.9 per cent. The data on origination of cases reveal a background of work on the part of private physicians, clinics, nursing service and other agencies.

The study of agency contacts previous to family-welfare agency control shows a high percentage in favor of the health-department nursing service; 48.1 per cent in Nashville and 38.9 per cent in Birmingham. Coöperation in dealing with cases also reveals a high percentage for the nursing service; 33.3 per cent in Nashville and 50.6 per cent in Birmingham. The percentages of families on which conferences were held were Nashville, 37 per cent and Birmingham, 61 per cent.

The figures on program of treatment are particularly revealing in the matter of relief (Nashville, 70.3 per cent; Birmingham, 51.9 per cent) and hospitalization (Nashville, 25.9 per cent; Birmingham, 42.8 per cent). My previous statement concerning the use of the Birmingham sanatorium seems somewhat belied by the fact that in Birmingham more

than 40 per cent of the family-welfare tuberculosis cases were hospitalized and 11 per cent were still on the waiting list.

In the study of unfavorable family conditions, the percentages on "refusal of hospitalization" (Nashville, 14.8 per cent; Birmingham, 15.6 per cent) and "refusal to stay in hospital" (Nashville, 7 per cent; Birmingham, 12 per cent) indicate the difficulties in this field. The fact that deaths during the period of case-work ran high (Nashville, 25.9 per cent; Birmingham, 22 per cent) shows that tuberculosis cases referred to family-welfare agencies, at present, are apt to be those in which desperate conditions have developed.

FINDINGS

This study of the two cities reveals a serious deficiency in tuberculosis work in the matter of the home preparation and follow-up work of discharged sanatoria cases, in both medical and social service. Discharged patients tend to relax their vigilance in self-care, and family conditions and problems frequently interfere with the patient's plans and needs. In neither city is the matter of vocational readjustment given adequate study and supervision. One is driven to the conclusion that the good of hospitalization is often largely dissipated by failure to stand by the patient and the family in personal, home and occupational adjustments during and after hospital care.

From the standpoint of social case-work, this study suggests the need of a more adequate integration of tuberculosis social work. We cannot expect to gain this merely by centralization, since individual agency initiative is valuable. But we can determine *areas of responsibility* and to a greater extent place family case-work responsibility *upon the agencies which have trained family case-workers.*

A further conclusion from this study, and perhaps most important of all, is that social work for tuberculous families should parallel the medical and nursing service. At present, family-welfare agencies, as the figures show, are not called upon to deal with tuberculous families until a sheer need for economic relief or for supplementary diet occurs. In other words, a misconception of family case-work prevails. The social problems of tuberculous families are so complex and the factors other than economic or diet relief so important that we cannot refrain from the conclusion that family case-work should be extended relatively to all tuberculous families. Just as the nurse has entree to all tuberculosis cases, so some method should be devised to introduce case-work

regardless of relief needs. This does not seem a wholly impossible program of initial visiting and subsequent follow-up where needs exist. To be sure, the program calls for integration of the work of the nurse and social worker, a division of labor between them and a unity of functions. The nurse neither has the time nor the specific training to undertake social case-work. And the necessity of socialservice continues even when the nurse's work is done. If, for the present, all clinical cases were referred simultaneously to the health-department nursing division and to the family-welfare agency for immediate follow-up, a more thorough tuberculosis control would result. Medical social work attached to tuberculosis clinics of the medical schools has already demonstrated that the extension of family case-work is feasible and productive of invaluable results.

And, finally, while the conclusion does not arise directly from the data of this study, I wish to suggest that a community's tuberculosis control program will not be adequate until the social causes, as well as the medical causes, of tuberculosis morbidity and death-rates are more thoroughly dealt with. These causes, about which we know all too little, centre about economic income, housing, family disorganization, occupational strain, the general level of culture in various classes, the traditions of local groups, and the general conditions which inhere in rural and city populations. The extension of social case-work for tuberculous families would bring much knowledge to light concerning such factors. At any rate, in the absence of any direct medical control or cure of tuberculosis, the situation demands a unified and an all-round attack.

THE DIFFERENTIAL DIAGNOSIS BETWEEN PULMONARY TUBERCULOSIS AND PULMONARY OR BRONCHIAL MALIGNANT NEOPLASMS[1]

CHANNING FROTHINGHAM

An accurate diagnosis is always desired, but in some instances it is of considerably more practical importance than in others. This is especially true in cases in which the diagnosis may be confused between two conditions which call for quite different procedures in regard to treatment. The two conditions mentioned in the title are examples of such a problem, because in the instance of tuberculosis there is always hope of recovery and, therefore, it is worth while to lay out a programme for treatment which may cause a considerable change in the patient's life. On the other hand, with our present knowledge, malignant disease in the lungs is practically a fatal disease and, therefore, it is unwise to subject the patient and the relatives to considerable inconvenience and expense in the search of a cure.

Malignant disease of the lungs, especially primary malignant disease of the bronchi and lungs, is becoming a more and more important problem because of the apparent increase in its occurrence. Whether this is due to an actual increase of the disease or to improvement in diagnostic methods and more frequent postmortem examinations is not clear, but a study of its occurrence at the Peter Bent Brigham Hospital in Boston is interesting. In the first ten years of the hospital's existence, 1913–1922 inclusive, the diagnosis of primary carcinoma of the bronchus or lung was made seven times. In the next five years, 1923–1927 inclusive, this diagnosis was made sixteen times, and in the next two years, 1928–1929 inclusive, the diagnosis was also made sixteen times.

On the other hand, an estimate in regard to the frequency of metastatic malignant tumor in the lungs is not easy to obtain at this hospital, because in many instances the metastatic tumors in the lungs produce no symptoms or signs and are only picked up at the autopsy. Most of the

[1] Presented by invitation at the twenty-sixth annual meeting of the National Tuberculosis Association, Memphis, Tennessee, May 8, 1930.

cases which come to autopsy after having died from diffusely scattered malignant tumors show metastases to the lungs. Clinically, however, this diagnosis of metastatic malignant tumor of the lungs has only appeared sixteen times in the records of the Peter Bent Brigham Hospital. These cases have been fairly evenly distributed throughout the existence of the hospital, although there has been a slight increase in frequency in the recent years.

Of the malignant neoplasms of the lungs and bronchi the primary carcinomata are the most fascinating to study because of the varied clinical pictures that they may produce. In some instances also, especially if the primary growth cannot be discovered, the metastatic tumors in the lungs present rather puzzling clinical problems.

Before this Association it is unnecessary to describe the clinical pictures which pulmonary tuberculosis may produce, and, therefore, in order to call attention to the differences between pulmonary tuberculosis and malignant disease of the lungs, it seems best to try to present to you as clearly as possible the different clinical pictures which malignant disease of the lung may produce and leave it to the members to note the points of difference between the two diseases. It must be kept in mind that this report concerns cases of pulmonary neoplasm which have been admitted to a general hospital and that, therefore, the clinical picture may be quite different from that produced by the same disease as seen in cases in the special bronchoscopic clinic to which they may have been referred earlier in the course of the disease. Purposely, neoplasms of the mediastinum and pleura have been omitted from this discussion, in order to emphasize the points that malignant disease of the bronchi and lungs bring out. The clinical pictures presented by primary malignant disease of the bronchi and lungs will be considered first and then the points of interest in regard to secondary growths.

The onset of primary carcinoma of the bronchi and lungs is insidious and the chief complaints from the patients upon admission to the hospital are quite varied. Thus in the 39 cases included in this study the chief complaints were cough in 12 instances, epigastric distress in 6, pain in the chest in 6, weakness in 5, cerebral symptoms in 5, shortness of breath in 4, symptoms due to metastases to the leg in one, and no symptoms referable to the carcinoma in one case which came to autopsy from another cause. In one of these 39 cases two complaints received equal prominence, making 40 chief complaints. The frequency of cerebral symptoms due to metastases from a primary growth in the chest occurring before the

primary growth gave symptoms is quite remarkable. In one instance at least in this group an operation upon the brain relieved the patient for several years from symptoms, and eventually the primary tumor in the chest became extensive enough to cause death. It is also interesting to note how different the chief complaint is even in those cases when it depends upon the primary growth in the chest. It seems safe to say that there is no outstanding initial symptom or character of onset which would justify one in more than suspecting a primary malignant growth in the bronchus or lung from the history of the case alone. The other points brought out in the histories are so varied, depending upon the extent of the growth, the stage of its development, its location and metastases, that no clear-cut history can be expected which will surely justify the diagnosis from the story alone.

Upon physical examination the interest centres upon the chest except in those instances in which abnormalities occur as a result of metastases. These signs due to metastases, of course, vary with the location of the metastases, and although frequently of unusual interest are not of practical importance so far as confusion with pulmonary tuberculosis is concerned. Upon examination of the chest the signs may be essentially normal or may be exceedingly varied in their abnormality. This will depend upon the size and position of the growth. In cases in which the growth is small there may be simply signs of a small area of infiltration; when it is large, but without obstruction to the intake or output of air, the signs of appreciable consolidation may be present. This will depend upon the size and position of the growth. In addition to the signs of an infiltrated or consolidated area in some part of the lung there may be present the physical signs appropriate for a displacement of the heart and mediastinum toward one side or the other, due to collapse of one lung because of obstruction to the main bronchus by the growth. This displacement is practically always toward the side upon which the tumor is. This obstruction may be in one of the branches of the main bronchus and thus complicate the picture more by only causing atelectasis of one lobe of a lung. A still more puzzling picture is found when the signs change from day to day, due to variation in the completeness of the obstruction to the bronchus. It is unusual for a tumor to displace the heart and mediastinum away from the side of the tumor in the manner that a pleural effusion does.

The clinical laboratory procedures in these cases are of very little help in making a differential diagnosis. There is nothing characteristic about

the sputum if any is present. In some cases the sputum may be blood-tinged or there may be definite haemoptysis. The leucocyte count is variable. In 24 of the 36 cases in which the leucocyte count was reported it was above 10,000 without anything of importance being noted in the differential count. In 12 of the cases there was no leucocytosis. In some of these cases tapping of the chest as a diagnostic procedure to rule out fluid was done, and in rare instances an examination of the small amount of bloody fluid which was usually obtained showed cells suggestive of carcinoma.

An examination of the temperature charts in these cases does not show any characteristic course of the temperature which could be used for determining the diagnosis. In many of the cases there was a little elevation of the temperature. Of the 36 cases in which there are satisfactory records the temperature was above 100° on several occasions in 13 of them. In 11 it often ranged between 99° and 100°, and in 12 cases the temperature was always below 99°.

Although suspicion of a primary carcinoma of the bronchi or lungs may be aroused by the history of the case, and the physical findings may add to the suspicion that something unusual is going on in the chest, very little help toward the diagnosis is obtained by the laboratory procedures or by following the course of the disease for a few days. Of tremendous value, however, is the examination of the chest by means of the X-ray. The X-ray pictures of the lungs in these cases vary markedly in relation to the size and location of the growth. The correct interpretation of these pictures is often exceedingly difficult. A comparison of X-ray pictures taken after a moderate interval may help to clear up the diagnosis in doubtful cases because these growths or the distortion they produce in the lung may change considerably in a short time. In those cases in which it is difficult to make the diagnosis of carcinoma of the lung or bronchus from the appearance in the X-ray picture help is sometimes obtained by studying the reaction to the therapeutic use of the X-ray. For, although many of the carcinomata of the lung do not respond to the X-rays, some of them do decidedly shrink after exposure to the rays. As other diseases in this location which cause shadows usually do not shrink after X-ray exposure, a reduction in size of the shadow may confirm the diagnosis. The accompanying series of illustrations are from X-ray pictures of cases of primary malignant tumor of the bronchi and lungs. These films were kindly selected by Dr. M. C. Sosman from the collection at the Peter Bent Brigham Hospital, Boston. They show how varied the pictures may be and emphasize certain points which are of diagnostic importance.

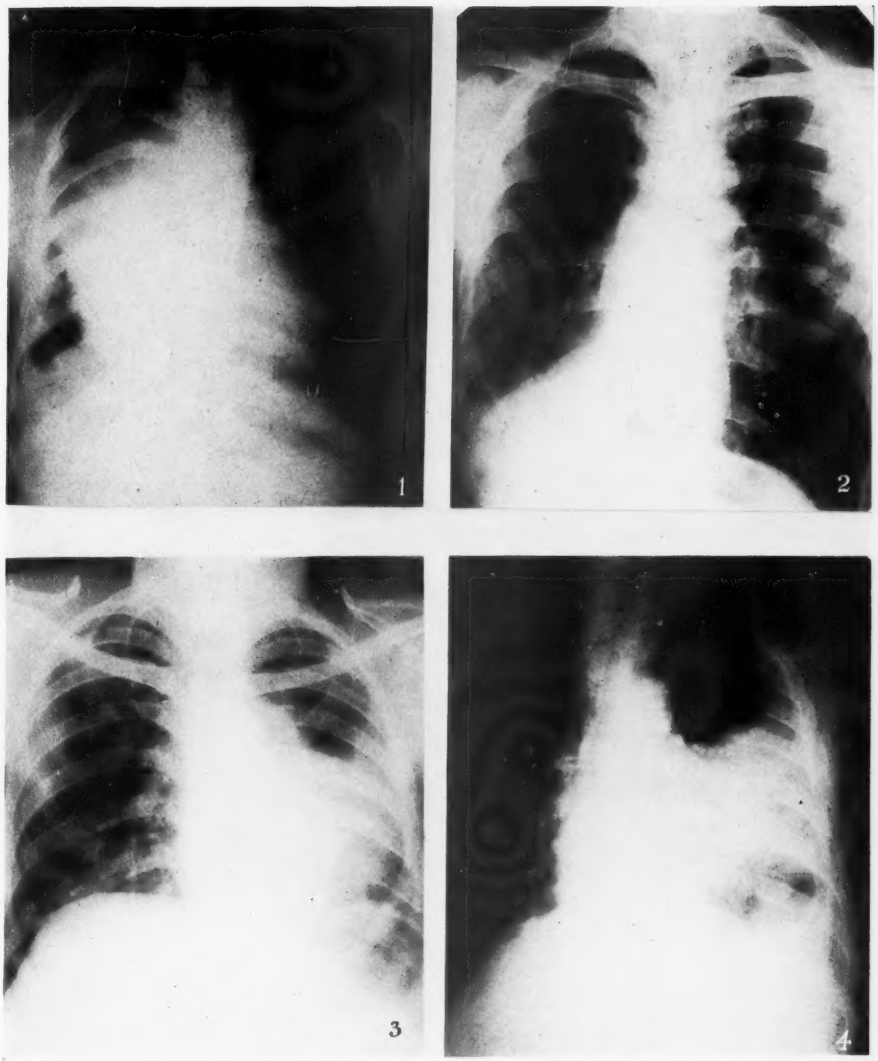


FIG. 1. (X-ray number 50,471, P. B. B. H.) A large malignant growth in the right lung. Lung tissue with air in it is seen above and below the tumor and also at its peripheral aspect. The heart and mediastinum are not pushed over to the left side. This tumor was resistant to the X-rays and did not shrink after therapeutic doses of X-rays.

FIG. 2. (X-ray number 47,840, P. B. B. H.) The tumor is just visible to the right of the shadow of the heart. Due to obstruction to the right bronchus the heart is displaced to the right, the right diaphragm is higher than usual in comparison with the left, and the trachea is displaced slightly to the right.

FIG. 3. (X-ray number 20,782, P. B. B. H.) This picture shows the shadow of the tumor and also indicates obstruction to the left bronchus because of the displacement of the heart toward the side of the tumor with the diaphragm on the left side also elevated.

FIG. 4. (X-ray number 35,651, P. B. B. H.) This picture also emphasizes the atelectasis produced by compression of the bronchus by the tumor, as indicated by the unusual elevation of the left diaphragm.

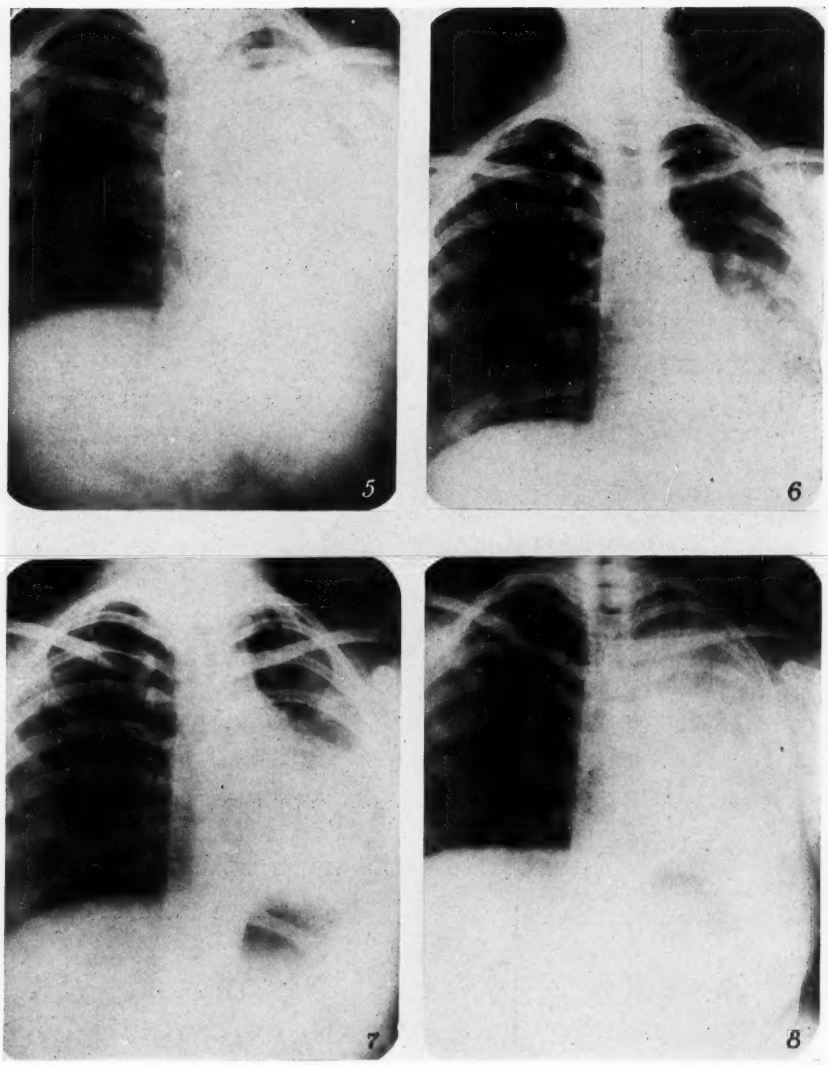


FIG. 5. (X-ray number 26,630, P. B. B. H.) This picture shows a dense shadow over the left chest, with the heart displaced toward the side of the shadow. In this picture it is not possible to say whether this shadow is produced by a growth or by atelectasis or both. Subsequent pictures (figs. 6, 7 and 8) in this case clear up the diagnosis.

FIG. 6. (X-ray number 26,630, P. B. B. H.) Same case as fig. 5 a few days later. More air is entering the left lung suggesting that the shadow in the preceding picture (fig. 5) was due in part to atelectasis produced by obstruction to the bronchus which has now partially let up. Shadow in his picture probably made up of tumor and a partially collapsed lung. Heart is still displaced toward the side with the tumor.

FIG. 7. (X-ray number 26,630, P. B. B. H.) Same case as figs. 5 and 6 at a still later date, showing a gradual extension of the tumor and an increase in the atelectasis of the left lung.

FIG. 8. (X-ray number 26,630, P. B. B. H.) Same case as figs. 5, 6 and 7, showing still further advancement of the disease and the atelectasis.

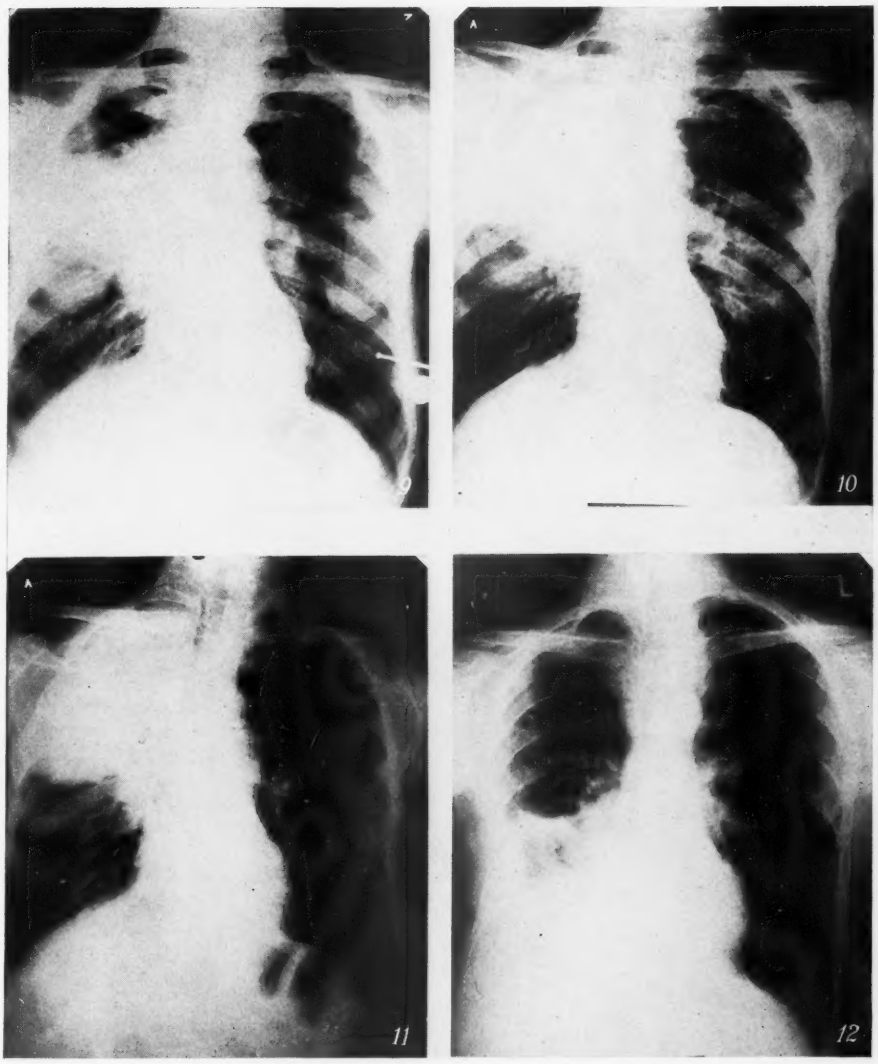


FIG. 9. (X-ray number 60,963, P. B. B. H.) A tumor of the lung, infiltrating from the hilum on the right, in which case there was some doubt about the diagnosis. Taken December 2, 1929.

FIG. 10. (X-ray number 60,963, P. B. B. H.) Same case as fig. 9, taken a week later, December 9, 1929, showing the rapid extension of the process which increased the suspicion of a malignant growth.

FIG. 11. (X-ray number 60,963, P. B. B. H.) Same case as figs. 9 and 10, taken about two and one-half months later, February 26, 1930, showing further extension of the growth in the right lung and also a soft tumor mass on the outer aspect of the left chest with metastases to an adjoining rib which settled the diagnosis.

FIG. 12. (X-ray number 52,485, P. B. B. H.) An extensive carcinoma at the base of the lung, with cavity-formation due to breaking down of the tumor.

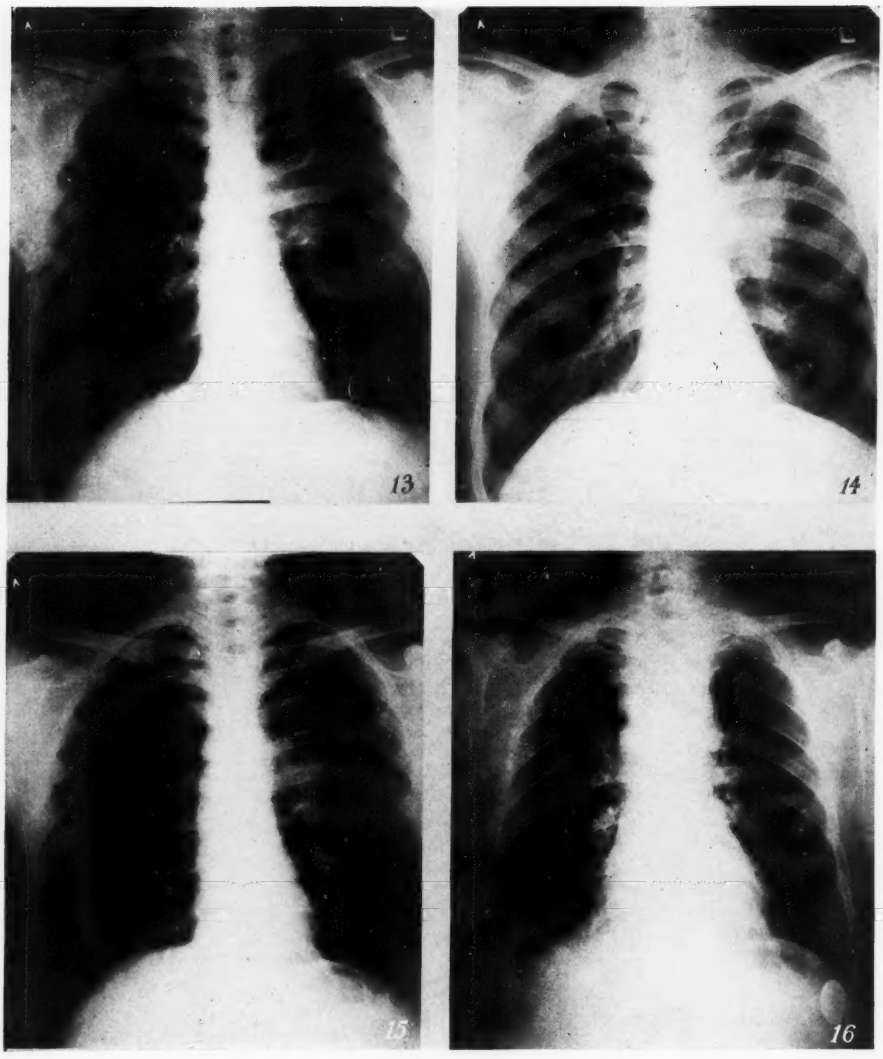


FIG. 13. (X-ray number 28,631, P. B. B. H.) A tumor growing in from the hilum on the left. The diagnosis at this date, December 13, 1929, was not settled.

FIG. 14. (X-ray number 28,631, P. B. B. H.) Same case as fig. 13, taken about six weeks later, January 30, 1930, showing a distinct increase in the growth.

FIG. 15. (X-ray number 28,631, P. B. B. H.) Same case as figs. 13 and 14, taken about six weeks later, March 17, 1930, showing the shrinkage produced by a therapeutic X-ray treatment over the shadow which confirmed the diagnosis of tumor.

FIG. 16. (X-ray number 60,462, P. B. B. H.) Primary carcinoma of the bronchus, which extended into the mediastinum and gave a picture similar to Hodgkin's disease.

From a survey of figures 1 to 18 it is obvious that primary malignant neoplasms of the lungs and bronchi may present a variety of X-ray pictures. It is also apparent that in many of them one cannot be sure that the shadow cast is due to a tumor, and that only after noting the changes in the shadow, as time goes on or after X-ray therapy, can a positive diagnosis be made. In still others no evidence of a tumor appears in the X-ray picture and the diagnosis is suspected from the distortion of the normal appearances of the chest due usually to some obstruction in the bronchus presumably caused by the growth.

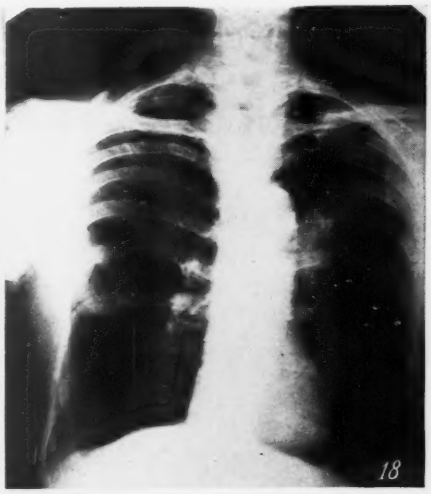


FIG. 17. (X-ray number 33,223, P. B. B. H.) Primary carcinoma of the lung, which produced an X-ray picture similar to pleurisy with effusion.

FIG. 18. (X-ray number 61,151, P. B. B. H.) Slight signs of old tuberculosis at right apex. Primary carcinoma at the left hilum which was not diagnosed during life. This patient died of metastases to the adrenals.

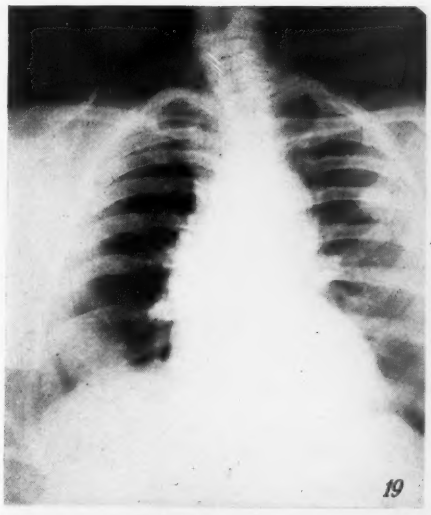
Fortunately, through the bronchoscope it is possible to actually see many of these tumors, especially the ones which show up least in the X-ray, because they are apt to be behind the heart or at the hilum and nearer to the large bronchi. Therefore, in all cases in which there seems a reasonable chance of any additional information by a bronchoscopic examination this should be done. In addition to looking at the suspected area, it may also be possible to obtain a bit of tissue for examination under the microscope and in this way settle the diagnosis.

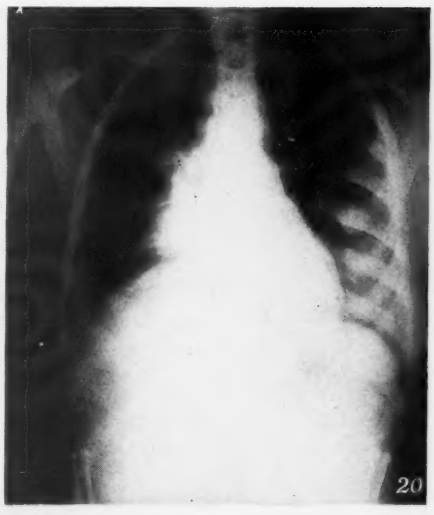
Although certain of these primary malignant tumors of the bronchi

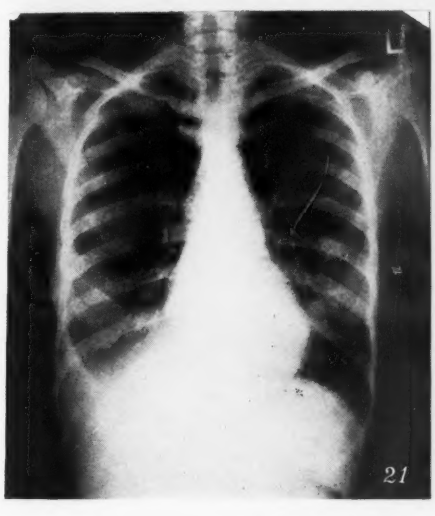
or lungs may simulate pulmonary tuberculosis in some one or several of their symptoms, physical signs or X-ray findings, the two diseases should not be confused if the possibility of primary malignant tumor is kept in mind and the case worked up thoroughly by X-ray studies and bronchoscopy. In certain cases the X-ray pictures must be repeated before a diagnosis can be reached and in other cases the reaction to X-ray therapy must be noted.

The problem of secondary malignant tumor in the lung may be relatively simple or quite complicated. Of course, the history of a previous diagnosis of carcinoma or malignant growth in some part of the body other than the lungs immediately arouses the suspicion of metastases upon the appearance of pulmonary symptoms, so that there is not much likelihood of the diagnosis being overlooked in such instances, although even under these conditions it is sometimes difficult to reach the proper conclusion from the complicated evidence that is present. It is a much more difficult problem, however, in those cases in which the primary tumor was not suspected before pulmonary signs or symptoms have developed or in which it cannot be found, even after the pulmonary condition suggests metastatic malignant tumor. A study similar to that of the cases of primary malignant tumor was made of the 16 cases found in records of the Peter Bent Brigham Hospital, in order to see if there are any typical clinical pictures of this condition which will easily lead to a definite diagnosis. Attention should be called also to the fact that in some instances metastases are found at autopsy in the lungs so small that they present no clinical signs or symptoms and, therefore, in a discussion of this sort they are of no practical importance.

In some of these cases of metastatic malignant tumor of the lungs the symptoms due to malignant tumor elsewhere in the body so overshadowed the pulmonary condition that the latter was relatively unimportant. In the 16 cases there were some instances in which the initial symptoms or chief complaints were multiple, so that more than sixteen chief complaints were found. In 7 of the 16 cases there were no symptoms noted in the chief complaint referable to the pulmonary metastases. The chief complaint was cough in 5 cases, pain in the side or chest in 3, shortness of breath in 1, and weakness in 2. Thus, as in primary malignant tumor of the lung, there is no characteristic complaint upon which to justify more than a suspicion of the disease. Also, in the more elaborate story of the past and present symptoms in these cases there was nothing which could be brought out to make a typical history for metastatic malignant tumor of the lungs.







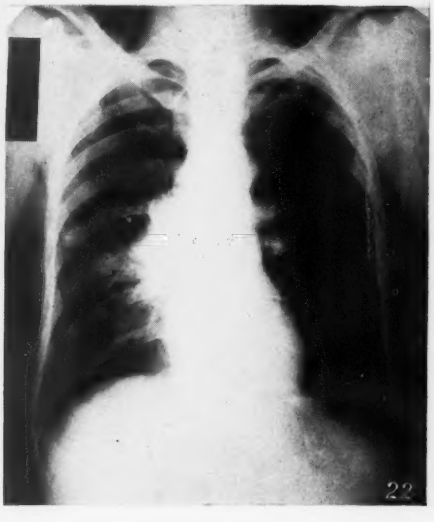


FIG. 19. (X-ray number 62,082, P. B. B. H.) Definite multiple tumors in the lungs.

FIG. 20. (X-ray number 58,831, P. B. B. H.) Definite tumors in the lungs. One side shows an absence of the breast shadow due to previous amputation.

FIG. 21. (X-ray number 55,384, P. B. B. H.) Diffuse metastatic haemangioblastoma which simulated miliary tuberculosis.

FIG. 22. (X-ray number 49,311, P. B. B. H.) Carcinoma, extending from the oesophagus into the lung at right hilum, with an inflammatory reaction resulting from a fistula between the oesophagus and the bronchus. Taken October 31, 1927.

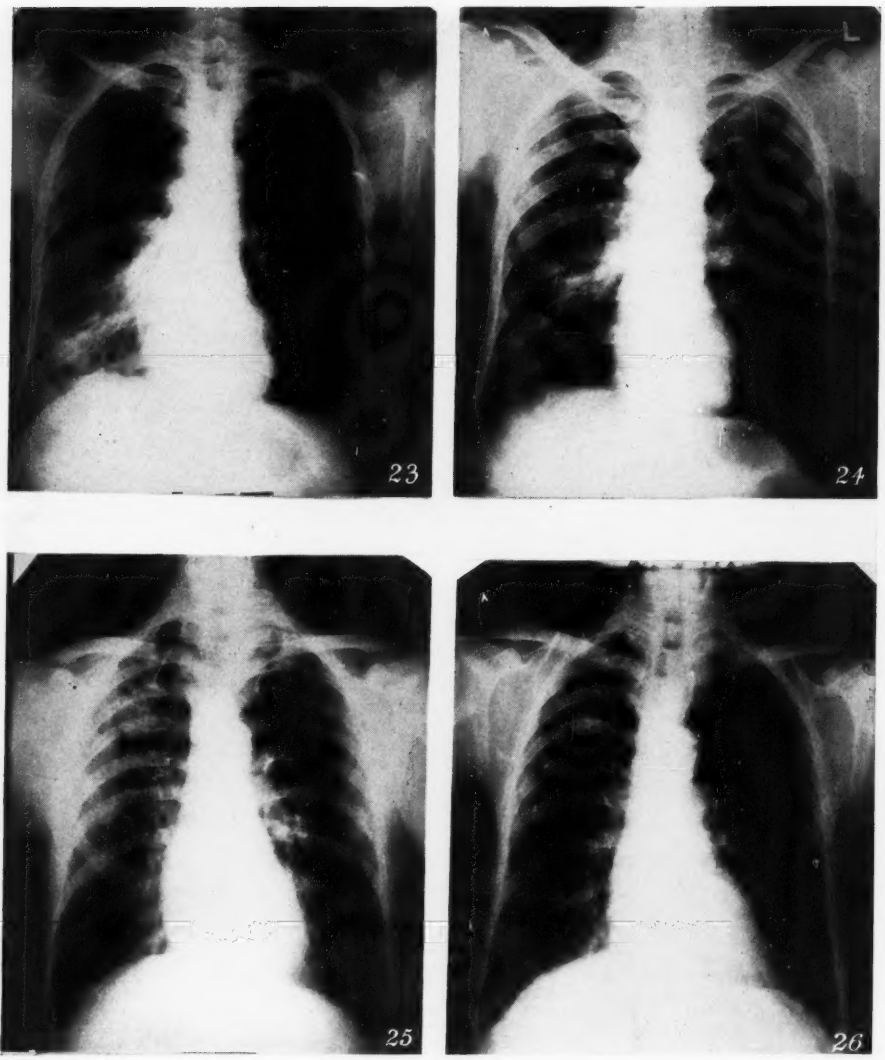


FIG. 23. (X-ray number 49,311, P. B. B. H.) Same case as fig. 22, taken November 11, 1927, showing extension of the process toward the base simulating bronchiectasis.

FIG. 24. (X-ray number 49,311, P. B. B. H.) Same case as figs. 22 and 23, taken November 21, 1927, showing a rather unexpected clearing of the process of bronchopneumonia resulting from the fistula between the oesophagus and bronchus.

FIG. 25. (X-ray number 49,631, P. B. B. H.) Taken November, 1927. Diagnosis uncertain. Suggests tuberculosis. Adhesive band at right apex with pulmonary emphysema or hydrothorax at that point.

FIG. 26. (X-ray number 49,631, P. B. B. H.) Same case as fig. 25, taken about eleven months later, October 29, 1928. Confusion with tuberculosis less in general appearance. Outgrowth from mediastinum has appeared. Ribs have become involved with metastases.

As in primary malignant tumor of the lungs, the physical examination in these cases did not show any characteristic signs which were peculiar to malignant disease, but a variety of signs existed, dependent upon the extent and location of the growths. In these cases of secondary malignant tumor the signs due to atelectasis of a part or all of one lung were not present, although it is reasonable to suppose that such might be the case.

The clinical pathology in these cases was not helpful in making a diagnosis as there were no persistent abnormal findings in the sputum, blood or urine. In 7 of the 16 cases the leucocyte count was over 10,000, while in the remaining 9 there was no leucocytosis. A study of the temperature curve also was of no diagnostic value, for in 5 of the cases the temperature was above 100° often, in 7 it was between 99° and 100° most of the time, and in 4 it was practically normal during the stay in the hospital.

As in cases of primary malignant tumor of the lung the diagnosis depended chiefly upon the X-ray examination. From some of the X-ray pictures the diagnosis of metastatic tumor could be definitely made. In other pictures the findings were more indefinite so that the diagnosis was obscure. Figures 19 to 26 bring out some of the X-ray features of metastatic malignant disease of the lungs. These films were also selected by Dr. M. C. Sosman from the collection at the Peter Bent Brigham Hospital, Boston.

If there is doubt about the diagnosis in metastatic malignant tumor of the lung a subsequent X-ray picture, taken in a short time, will usually clear it up. In this condition bronchoscopic study is usually of little benefit, as in the great majority of cases the growths are out of sight from the bronchoscope. Should they be within range of vision a bronchoscopic study may help to settle the diagnosis. As in primary malignant tumor of the lungs a careful study of the case, with special regard to the X-ray findings, should bring out a clinical picture that will not be confused with pulmonary tuberculosis.

THE DETERMINATION OF TUBERCULOSIS AND TOXIC GOITRE[1]

STEWART R. ROBERTS[2]

This differentiation deals only with two conditions: first, chronic pulmonary tuberculosis, and, second, toxic goitre. Acute miliary tuberculosis, with its severe and dramatic picture, including ten per cent or less of all pulmonary tuberculosis, does not enter this discussion. Toxic goitre includes two types: the exophthalmic goitres and degenerative adenomata with hyperthyroidism. Simple struma, colloid goitre and adenomata without hyperthyroidism, all nontoxic, are not considered. A clinician, mentally running, may easily read a well developed and advanced case of either tuberculosis or of toxic goitre. If he should stumble as he read, another examination of the patient, with or without the laboratory, would quickly start him off again. The incipient cases, the ones that insinuate themselves so timidly that a clear clinical announcement of their nature is lacking, are the difficult ones.

This is an old and mooted question. Formerly the differentiation was much more difficult than it is to-day. Indeed some clinicians hold that the difficulty is far overrated. The difficulties thirty years and more ago, however, were certainly not overrated. The awareness then as to the signs and symptoms of early tuberculosis or of early hyperthyroidism were not the common possession of the profession as they are to-day. The awareness of the profession has been greatly increased, and then, too, we have the use of the X-ray and the value of the basal-metabolic rate. So far as the X-ray is concerned there is only one difficulty and that is its interpretation. How often do we hover over stereoscopic plates of the chest trying to decide pro or con, and in the doubtful cases we hover long. Fluoroscopic examination shows movement primarily, and with an advanced lesion is helpful. In early or doubtful cases the stereoscopic plates are better, and it is often well to compare stereoscopic plates with one flat plate, for the last with everything in one plane may by contrast

[1] Read at the twenty-sixth annual meeting of the National Tuberculosis Association. Memphis, Tennessee, May 8–10, 1930.

[2] Atlanta, Georgia.

be helpful. It is well to remember, however, that the X-ray may exclude tuberculosis and may show no lesions, even though tubercle bacilli are found in the sputum. Then the X-ray may reveal lesions that appear tuberculous even though the individual is not or never has been ill. With a good history, a good stethoscope, much experience, careful examination, stereoscopic plates and a good laboratory, one should be able to diagnose a case of early tuberculosis, provided he be neither too dogmatic nor too open-minded nor too hesitant toward the cumulative evidence of the case. Three definite signs in early tuberculosis revealed by the stethoscope are always to be borne in mind by the clinician,—rough granular breathing, persistent crepitant râles, and distant or repressed breathing. It is necessary for the clinician to decide whether one or more of these signs be present. If he be experienced he may decide so automatically as to be unconscious of his decision. These appear to be reasonable statements, and yet Fremont-Smith reports a case in which the reasoning appeared true. The case was decided not to be tuberculous, and yet six months later a pleurisy with effusion made the diagnosis and confirmed the error. Time alone may decide certain cases.

The awareness of the profession toward hyperthyroidism is much keener than ever before. We have all and more to diagnose goitre than we have ever had, and then we can measure the basal-metabolic rate. This laboratory procedure, however, involves preparation, a good technician, a reliable instrument and favorable conditions. Men seem to make poorer subjects for the test than women. Two tests seem better than one. If tuberculosis is suspected, the test, as usual, should be done in the early morning and the patient should be afebrile. The afebrile patient with tuberculosis usually has a metabolism within normal limits. The interpretation of the metabolic test should be full in the face of the clinical studies, and at least two weeks should have elapsed after the administration of Lugol's solution. I am convinced that there are certain cases of hyperthyroidism, with the ordinary instruments used, that may show readings within normal limits, and yet hyperthyroidism exist in the patient. It is one thing to have hyperthyroidism in the test and it may be another thing to have it in the patient. The instrument is certainly a great aid in differentiating between early tuberculosis and mild hyperthyroidism but the readings are to be related to the clinical condition.

A discussion of the ordinary clinical signs and symptoms, though partaking of the elemental, is by contrast somewhat impressive. It is well to remember that certain individuals, particularly women, have by nature

what may be called a "thyroid constitution." Their eyes are bright, their reaction is emotional, the pulse normally fast, the mind acts quickly, and every movement is unduly animated. Let a young women of eighteen to thirty present herself for examination, particularly if she have a long thin neck, with a visible thyroid or one lobe easily palpable by slipping the thumb over the inner border, a rapid pulse, a slight fever, a history of lassitude and weakness, and easy perspiration, and one's diagnostic mind faces action and decision.

1: Temperature: From our youth we are impressed with the fact that the normal temperature for the normal individual is 98.6°F. Any variation above this is called fever and any variation below is called a subnormal temperature. The reading probably represents the average temperature of the race rather than the normal temperature of the individual. It is one thing to have fever and another to have a slight rise above 98.6°. In the South in the summer most women under forty, coming to the office for examination, show a rise above the average. The tuberculous patient is apt to have more fever than the patient with an early goitre. The afternoon rise is more common in both than a morning rise, except in a thyroid crisis. I rarely see any temperature in goitre that is at all diagnostic of the condition. The contrary is of course true in tuberculosis. Furthermore, the taking of accurate temperature is difficult. In hard cases a rectal temperature is better. A five-minute mouth temperature with the same thermometer is well for a check. We have noticed that patients entering the hospital with afebrile conditions or strangers coming to the office for examination with afebrile conditions frequently show a temperature of 99.5° to 100.0°. It is probably to be interpreted as an entrance temperature from the subjective emotional reaction. Roger Lee reports a case of hypothyroidism whose outstanding symptom was fever.

2: Circulation: The blood count is notoriously of little assistance. In both conditions a mild secondary anaemia may be present, a moderate leucopoenia, and a relative increase in the lymphocytes and monocytes. In goitre a lymphocytosis may be rather more marked and may be absolute as well as relative, but the same remarks apply to asthenic individuals without either disease. I am more and more impressed with the aggressiveness of the lymphocytes in patients in the South, particularly under thirty and over sixty. The blood picture may be of little or no assistance. The leucocytic reaction in tuberculosis is not specific. Clinical diagnosis is first necessary before the interpretation of leucocytic

count is of real value in interpreting the state of the tuberculous process. Three types of leucocytes are to be taken into consideration: the neutrophiles, ranging around a mean of 65 per cent; lymphocytes, ranging around a mean of 20 per cent; and mononuclears, ranging around a mean of 5 to 8 per cent. The eosinophiles and basophiles seem not related to the tuberculous process. Medlar's extensive work on this problem is well worth reading and testing.

The difference in blood-pressure is really valuable. In tuberculosis the average blood-pressure tends to fall from 10 to 40 per cent below that previous to the disease. The pulse is of small volume, indicating a small cardiac output, and therefore the spread of the pulse-pressure is low, usually below forty. Whereas, in goitre there is a large cardiac output which is an association of the increased metabolism, there is a relaxation of the muscle coat of the arteries, the arterial bed is relatively wide-open, and the systolic pressure is increased, the diastolic decreased, and the pulse-pressure notably increased. The pulse-pressure is apt to be 60 or above. A pulse-pressure of 60 or above, associated with a persistent tachycardia, points strongly to goitre. The blood-pressure is apt to be as persistent as the pulse-rate.

Much can be said of the heart in early goitre. Many adjectives are needed here. It is at least in early goitre a strenuous, exhilarated, overactive heart, and that usually without murmurs. It seems excited beyond all reason. It is usually a heart of acceleration as well as of palpitation. The patient is conscious of the bird-in-hand effect in the chest. The loudly accented, slapping, mitral closure, the rapidity, the easy transmission of the valve closures to the palpating hand, form one of the most suggestive pictures in medicine. I have never seen a heart in tuberculosis so characteristic of that disease as is the speed heart in goitre.

In tuberculosis the pulse-rate is apt to range from 80 to 100 and may rise 10 to 20 beats with mild psychic or motor activity. At rest, it rests; whereas in goitre the pulse is persistently rapid, with less notable variation on psychic or motor excitement.

3: Tremor: Tremor is more pronounced in goitre; the skin more flushed, dermographia more frequent and mild itching more common. Rosenbach's sign, a coarse tremor of the upper lids with the eyes shut, is an extremely valuable clinical sign in goitre. It may occur slightly in asthenia or in tuberculosis or in any weakened state, but I think never with the persistent and dramatic rhythm that it does in goitre. To me it is often a last sign at the parting of the ways. It has been my experience

that sweating in tuberculosis seems overmuch in the arm pits, and proportionately less elsewhere; whereas in goitre the moist skin is more universal, except of course in the night-sweats of tuberculosis, and even they are often rather limited.

A whole chapter could be written on the eye in the two conditions. The eye of the thyroid constitution is bright and sparkling. The eye of tuberculosis is often unusually bright and sparkling, but with it may go a hint of weakness in the features and pallor above the normal. In goitre the eye is bright, the Rosenbach sign present, and perhaps also one or more of the classic eye signs of goitre. One is inclined to agree with Musser that the specific tests of tuberculosis have been somewhat neglected in making a differential diagnosis. He advises against the intracutaneous or subcutaneous injection of tuberculin in goitre, but believes that the cutaneous test of Pirquet or the percutaneous test of Moro are specific reactions. As is well known, many adults have had previous minimal tuberculous infection and a definite reaction is not so important. But when the tests are negative it is of great value, particularly when a first-stage tuberculosis is suspected.

Digestive disturbances seem more common in tuberculosis than in goitre. Indeed in early goitre a good appetite is the rule, whereas anorexia or even actual repulsion toward food is common in early tuberculosis, in the neuroses and in pellagra. Diarrhoea may rarely occur in either condition, but it is certainly not characteristic of incipient states. There is loss of weight in both conditions, but in tuberculosis the loss is associated with a loss of appetite, whereas in goitre it is associated with a normal to increased or even voracious appetite. Good eating, tachycardia and loss of weight suggest goitre. The psychic state in the two conditions, while highly variable, is at least suggestive. I have seen a first-stage tuberculous patient play abnormally good golf, show excessive drive in his work, perspire easily and be rich with blood, but the tachycardia and irritability of the goitre patient were lacking. He still possessed an intellectual reaction to life and the blood-pressure was lower than normal. His rainbow was hope, and all his efforts would be rewarded. The goitre patient may have drive, but not as much languor as the average tuberculosis patient, and more irritability, and the tuberculous patient is not so emotional as one with goitre.

On the whole, as Musser well says, there is more chance of calling an early tuberculous patient a thyroid case than of calling an early thyroid case tuberculosis. It is no rare finding to see the scar of a thyroidectomy

on the neck of inmates of the tuberculosis sanatoria. Pettit found three in his 45 inmates. The theory that the toxins of tuberculosis may precipitate a hyperthyroidism seems not substantiated. Thyroids do become infected with tuberculosis, but clinically the condition is not susceptible to diagnosis. Stanton found four such thyroids in 26 thyroids of persons dead of tuberculosis. The thyroid in tuberculosis is unquestionably often enlarged, but one sees it enlarged in health, particularly in young women. The enlargement may be more apparent than real, owing to the emaciation or to a long neck in a thin individual. Furthermore, the eye signs of hyperthyroidism are not a rarity in early tuberculosis except the Rosenbach sign. Any one case may be exceedingly difficult to decide, and even watchful waiting may be the best diagnostician. On the whole, however, with facilities at hand, the experienced clinician will not have great difficulty with the average case of either tuberculosis or hyperthyroidism. It is to be remembered that active pulmonary tuberculosis and hyperthyroidism do occur in the same patient at the same time. I have been impressed with the occurrence of degenerative adenomatous hyperthyroidism and cancer of the breast at the same time. With an early tuberculosis associated with an active hyperthyroidism as a rule, in skilful hands, a thyroidectomy may be done with relative safety and the patient then proceed to the cure of his tuberculosis. A summary of diagnostic points to distinguish the two conditions may be of assistance, as follows:

1. A careful history, with accent upon exposure to tuberculosis as contrasted with emotional strain and family goitre.

2. A careful physical examination, contrasting the lungs of tuberculosis with the heart of goitre, and similar contrasts between the pulse of each condition, the blood-pressure, the eye, the tremor, the skin and the amount of food eaten contrasted with loss of weight.

3. The process of critical contrast should occur in the minds of the clinician.

4. The presence or absence of bacilli in the sputum.

5. The skin test, if necessary, for tuberculosis.

6. A contrast of the stereo plates with the basal-metabolic test.

7. A critical analysis of the results in hand and a restudy of the patient should eliminate the present ratio of error, which is about 0.5 per cent.

8. A critical attitude toward the blood, with particular accent on the count and interpretation of the polymorphonuclears, lymphocytes and mononuclears.

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INTRATHORACIC PRESSURE STUDIES IN TWO TYPES OF VALVULAR SPONTANEOUS PNEUMOTHORAX

STANLEY J. G. NOWAK AND EDWARD D. CHURCHILL[1]

Pneumothorax following a spontaneous or traumatic rupture of the surface of the lung may produce profound respiratory distress, or, in contrast, may occasion so slight a disturbance that it passes unnoticed by the patient. In the uncomplicated case the lung collapses as air passes into the pleural cavity, and the contraction of the elastic pulmonary tissue closes the rent in the pleural surface. Healing soon obliterates the communication between bronchial tree and pleural cavity, and absorption of the air is accompanied by reëxpansion of the lung.

In the presence of pleural adhesions the tear on the surface of the lung may be held open. Coughing and other forceful expiratory efforts force air into the pleural cavity under considerable tension, building up a positive pressure. Under these circumstances the condition is referred to as a "tension" or "valvular" pneumothorax. The positive pressure may be raised still further by the outpouring of a fluid exudate or the occurrence of a haemorrhage into the pleural cavity.

Interstitial or subcutaneous emphysema is a frequent complication of a tension pneumothorax. It occurs when the tear in the lung is accompanied by a rent in the parietal pleura, as is the case when a fractured rib is driven into the lung. The compressed air forces its way into the soft tissues of the chest-wall and mediastinum, spreading even as far as the extremities. The air may gain entrance to the loose tissue spaces of the mediastinum by dissecting through the interstitial or subpleural pulmonary tissues. It then makes its appearance superficially at the upper outlet of the thorax to permeate the cervical and supraclavicular tissues.

Tension pneumothorax almost invariably causes an extreme degree of respiratory distress and circulatory embarrassment. Relief of these very urgent symptoms may be accomplished with dramatic suddenness by performing thoracentesis with a needle of large calibre. The air will at times be found under a positive pressure that will violently force the barrel out of the syringe. Temporary relief is afforded by allowing the air to escape, but if the pneumothorax is of the true valvular type the pressure

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is soon built up again following withdrawal of the needle. By attaching a section of rubber tubing to the needle and placing its end under water the existence of a valvular opening in the lung may be ascertained. If bubbles of air constantly escape from the tube during quiet expiration it will be found necessary to provide for more prolonged decompression by inserting a small catheter through the chest-wall. The end of the catheter is attached to a tube which is kept sealed by a water-valve. As soon as air ceases to bubble out of the tube with expiration the catheter may be removed from the chest, provided, of course, that a complicating empyema has not developed in the meantime.

The following case history illustrates the clinical course of a patient with tension pneumothorax complicating pulmonary tuberculosis, and provides a record of the actual pressure readings in a typical case.

A man, aged 31, was admitted to the Boston City Hospital for cough, weakness, and night-sweats for the preceding eight months, during which time he had lost 25 lbs. in weight. His cough was productive of purulent sputum, occasionally blood-streaked. On admission the patient was acutely ill, coughing continually and drenched with perspiration. Examination of the lungs showed diffuse involvement throughout the left with a loud friction rub. X-ray films on admission showed extensive tuberculosis of the left lung with a small cavity below the clavicle and consolidation in the midchest. The sputum contained tubercle bacilli.

For 8 days the course of the disease was that of a severe pulmonary and pleural tuberculosis, with fever varying between 99.8° and 103.8°, pulse from 110 to 120, and respirations from 20 to 35. On the 9th day the patient complained of severe pain in the left intraclavicular region accompanied by dyspnoea. Physical examination and X-ray films showed a left-sided pneumothorax. On the 10th day dyspnoea and cyanosis increased, and temporary relief was obtained by a chest tap. A positive pressure in the intrapleural space was evidenced by the force exerted on the plunger of the syringe. The tap was repeated during the night and as an emergency measure the needle was left in place. The following morning a catheter was inserted in the back between the 7th and 8th ribs by means of a trocar. Pressure readings, taken by a water manometer, were +8.5 cm. on inspiration and +14 cm. on expiration. By using an inverted graduate as an air trap and allowing air to bubble out the end of the catheter the following pressure readings were taken:

	Inspiration	*Expiration*
Initial pressure	+8.5 cm. to	+14 cm.
After removal of 250 cc. of air	+7 cm. to	+10.5 cm.
After removal of 500 cc. of air	+4 cm. to	+8.5 cm.
After opening catheter to atmosphere	+1 cm. to	+7 cm.

After decompression of the chest, the average output of air per breath through the catheter was 3 cc. On coughing approximately 10 cc. of air was forced out through the end of the catheter.

Two bottles containing water were connected with the end of a catheter. Their arrangement is shown diagrammatically in figure 1, disregarding for the moment the faucet suction-pump attachment. Bottle A was employed as a water-valve, permitting the air to be forced out under the water seal. Bottle B served simply as a fluid trap to prevent aspiration of the water from bottle A into the chest and also to collect any pleural exudate. As a matter of fact a frank empyema was encountered in this patient so that foul pus was immediately collected in bottle B.

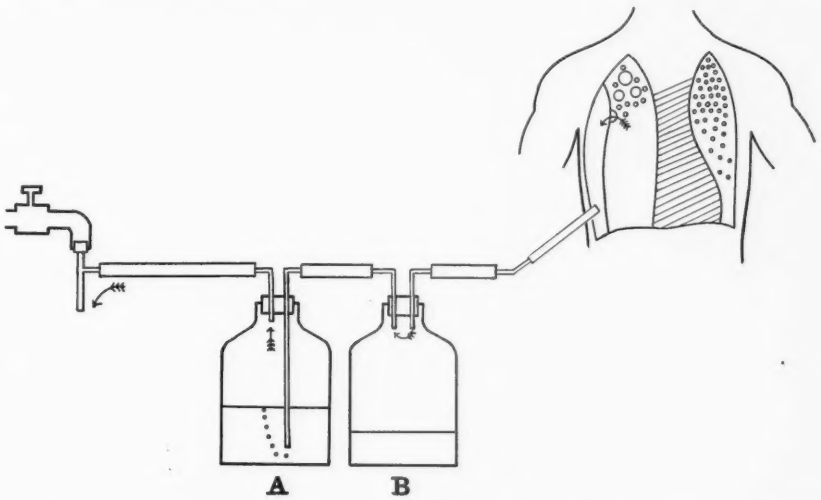

FIG. 1. Suction apparatus used in the second case. In the first case the faucet suction-pump attached to the far side of bottle A was not employed, as the air, because of its positive pressure, was expelled without the aid of suction.

Dyspnoea and cyanosis continued, however, and the patient died on the 13th day, five days after the onset of the pneumothorax.

Dyspnoea and respiratory distress, accompanying the onset of a spontaneous pneumothorax, by no means indicate that the air in the pleural cavity is under tension. If the vital capacity of the patient is greatly reduced by a bilateral process, the sudden occurrence of even a small pneumothorax on one side may initiate the most profound symptoms of respiratory distress. Further, it is impossible to effectively relieve these symptoms by simple aspiration if the bronchial fistula remains patent. A second case history will illustrate just such a set of circumstances.

A colored man, aged 26, was admitted to the Boston City Hospital for respiratory distress. His pulmonary tuberculosis had advanced rapidly during the preceding year, so that in addition to extensive cavitation at the right apex he had a diffuse exudative or pneumonic lesion throughout the left lung. Two

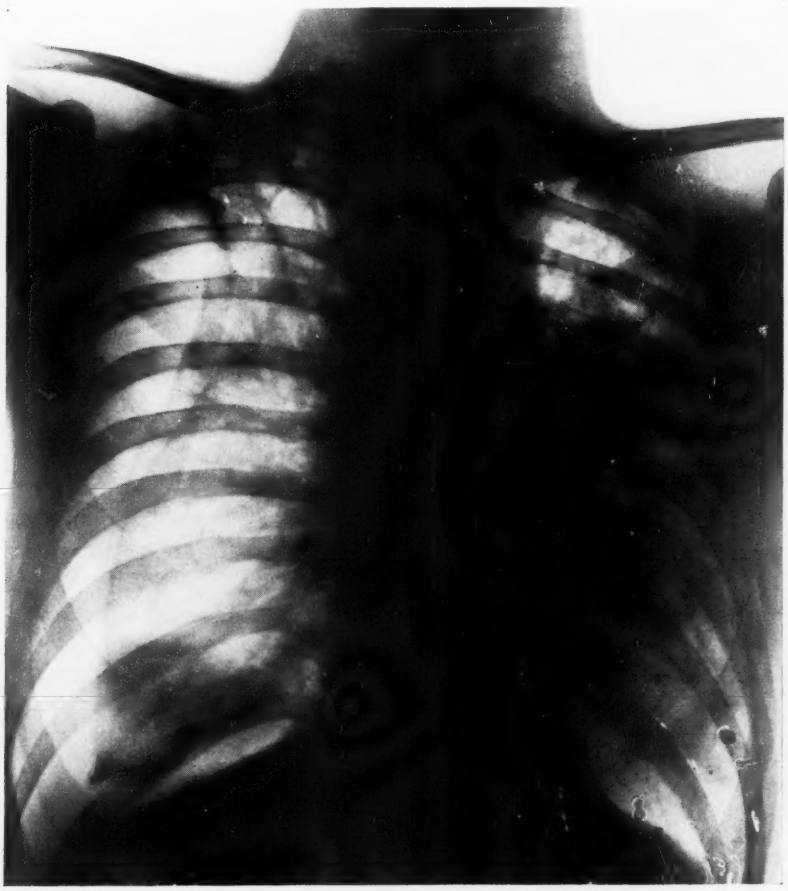

FIG. 2. X-ray film of second case on admission showing pneumothorax and apical cavitation on right and extensive involvement on the left.

weeks before admission he experienced a sudden onset of choking and dyspnoea. The difficult breathing and extreme orthopnoea continued without remission. When examined in the medical ward he was found sitting on the edge of the bed, extremely cyanotic and breathing in short ineffectual gasps. His temperature was 101°, pulse 100 and respirations 32. X-ray examination (figure 2),

as well as the physical findings, demonstrated a diffuse infiltration of the entire left lung. The right lung was partially collapsed by a pneumothorax, and cavitation was evident in the adherent apex. The heart and mediastinum were displaced to the left. Fluid was present in the pneumothorax.

It seemed obvious that the spontaneous pneumothorax involving the better lung had so reduced the respiratory function that the patient was dying of asphyxia. This was true despite the fact that the pneumothorax was of such a size that it might well have passed unnoticed had the contralateral lung been normal. With the disease in the contralateral lung, however, the reduction in intrapleural negative pressure combined with the actual collapse of functional lung produced the severe respiratory distress pictured above.

Fluid to the amount of 720 cc. and several syringefuls of air were withdrawn from the chest with a needle. A temporary relief of the dyspnoea was experienced. Two further withdrawals of air were found necessary because of recurrence of the urgent symptoms. It was evident that the tear in the lung was being held open by adhesions allowing the pneumothorax to reform. It was also evident that the air in the pneumothorax was not under positive pressure and that simple insertion of a catheter with a water-valve would not be adequate treatment. The X-ray films suggested this lack of positive pressure by showing only partial collapse of the nonadherent portions of the lung, and the chest taps confirmed the lack of positive pressure, as the air had to be sucked out with a syringe.

A direct determination of the intrapleural pressure was then made with a manometer. The excursions were from -3 cm. of water on inspiration to $+1$ cm. on expiration. In order to bring relief to the patient under these circumstances it became necessary to withdraw air from the pneumothorax at a more rapid rate than it was able to enter the chest through the hole in the lung. By such a procedure the negative pressure was increased and the effective lung volume augmented.

With air-tight technique a catheter was inserted in the 5th interspace well below the level of the apical pleural adhesions. The catheter was attached to an ordinary suction bottle (figure 1) with a second bottle interposed for additional safety. Suction was obtained by means of a water suction-pump attached to a faucet. The suction was so regulated that air bubbled from the long tube under water in the bottle on expiration while the water rose a short distance in this tube on inspiration. The interposed safety bottle served as a safeguard against possible aspiration of water from the suction bottle on inspiration. It also collected any pleural exudate, the accumulation of which in a single bottle apparatus alters the pressure relations by changing the water-valve.

After starting gentle suction the intrapleural pressure, as measured by a water manometer, varied between -4 and -6 cm. on inspiration and $+1$

and 0 on expiration. On increasing the suction the pressure was lowered to excursions as low as −8 cm. to −4 cm.

The relief effected by this apparatus was immediate. The orthopnoea disappeared so that the patient could lie flat in bed. X-ray films taken on the next day (figure 3) showed practically complete expansion of the lung.

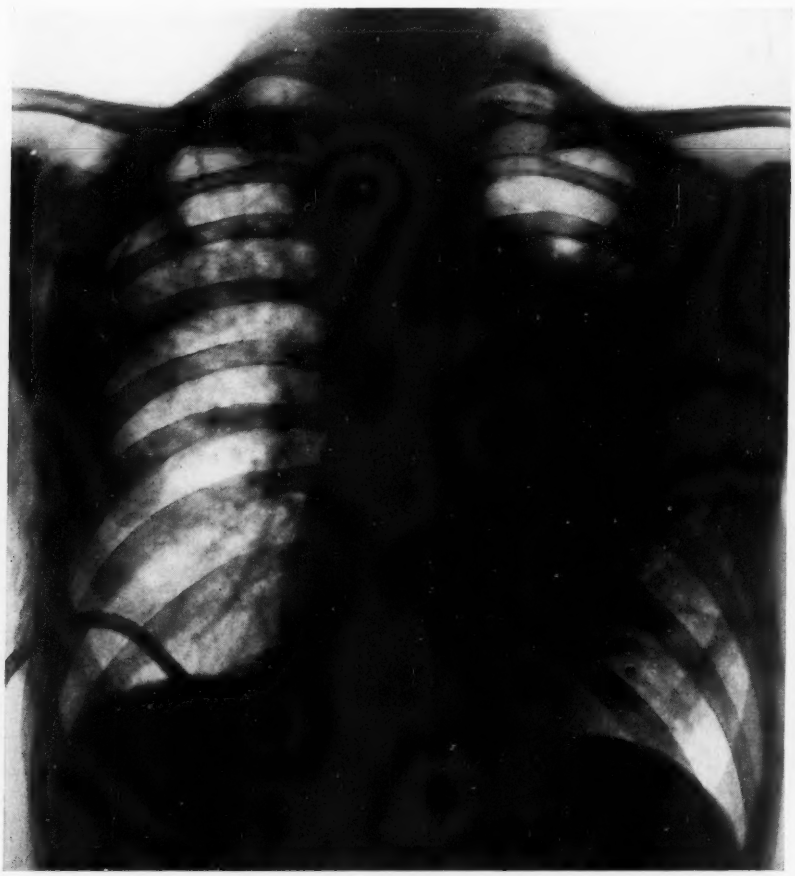

FIG. 3. X-ray film of second case during suction treatment. The right lung is fully expanded. The left shows the same extensive involvement.

The only part of the apparatus which required fairly constant attention was the catheter, as it became plugged with fibrin from time to time. It was also found that air ceased to flow when no plugging of the catheter could be demonstrated. This effect may be explained by closure of the catheter tip between a completely expanded lung and the chest-wall. This explanation was borne out

by the fact that the apparatus would spontaneously resume drawing off air whenever a slight amount reaccumulated.

About 12 days after thoracotomy the effusion became definitely purulent in character, with drainage of a small amount of thin pus into the safety bottle. This infection from the bronchial fistula was inevitable. The drainage was adequate, however, as X-ray films gave no evidence of an accumulation of fluid. The patient's condition grew gradually worse, and death occurred two weeks later from tuberculous toxaemia.

Direct observation of the venous pressure before and after instituting treatment showed a marked improvement in the degree of circulatory embarrassment. The spontaneous pneumothorax interfered with the important rôle that the intrathoracic negative pressure plays in promoting venous return to the heart. Under these conditions the venous pressure in the arms reached the abnormal height of 17 to 18 cm. of water. On the day after suction was started the venous pressure ranged between 9 and 13 cm. of water.

SUMMARY

The physiopathology of tension pneumothorax is discussed and illustrated by actual pressure readings from a patient in which this lesion occurred as a complication of pulmonary tuberculosis. The treatment by closed thoracotomy is discussed. The case of a second patient is described in which marked respiratory distress and circulatory embarrassment attended a spontaneous partial pneumothorax. The pneumothorax was "valvular," but the air was not under tension. Aspiration of the air was followed by rapid reaccumulation, and a study of the pressures showed that the insertion of a catheter alone would be inadequate. Recourse was had to thoracotomy with constant suction. The relief of dyspnoea and circulatory embarrassment was immediate. Manometric readings and venous-pressure determinations are cited to illustrate the essential pneumatic and haemodynamic principles under consideration.

CYSTINURIA AND TUBERCULOSIS

HOWARD B. LEWIS AND MARIE F. O'CONNOR[1]

Attempts to explain the origin and significance of the metabolic "error," cystinuria, have not resulted in any entirely satisfactory theory (1). It has been shown repeatedly that the ingestion of diets high in their protein content increases the urinary excretion of cystine (2). This has led to the suggestion that the cystine excreted is exogenous, originating from the cystine of the protein of the diet. However, the fact, that the administration of the amino-acid cystine itself to a cystinuric does not influence in any significant way the elimination of urinary cystine, makes necessary some modification of the theory of exogenous origin. It has accordingly been suggested that the protein is not completely hydrolyzed to amino acids in the gastrointestinal canal, that a portion of the cystine is absorbed in conjugated form as a peptide or similar protein derivative and that from a compound of this type the urinary cystine is derived. No proof in support of this theory exists however. The possibility of an endogenous origin of a considerable portion of the cystine excreted by the kidneys has also been indicated (3). Brand (4) has offered evidence of the existence of a cystine complex in the urine which, after the secretion of urine, by hydrolysis may give rise to the cystine observed in cystinuria. His theory does not, however, explain why such a complex (possibly glutathione or a similar peptide containing cystine) should be eliminated by the kidneys in significant amounts in cystinuric urine, but not in normal urine. The origin of the "error" is thus obscure.

Of especial interest is the case reported by Magnus-Levy (5) in which the maximum excretion of cystine was associated with an infection which produced a marked rise in body temperature. After the cure of the infectious process, the cystine excretion fell to a low level. This suggests a relation of the cystinuria to some endogenous metabolic process, which was influenced by the febrile reaction occasioned by the infection. Sylla (6) has also noted a relation between fever and the excretion of cystine.

In cystinuria the organic sulphur fraction (the so called "neutral"

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sulphur) of the urine, normally present in very small amounts, is much increased since cystine contains sulphur in unoxidized form. Suggestive increases in the organic sulphur of the urine have been observed in many pathological conditions, particularly in cancer and in tuberculosis (7). These increases in the organic sulphur have not been considered to be related specifically to the diseased condition but to be due to some impairment of the oxidative processes of the body.

Monceaux (8) in a recent study of the organic sulphur fraction of the urine in tuberculosis has concluded that an important constituent of this fraction is cystine, which he was able to isolate in crystalline form from more than 40 per cent of the urines of tuberculous patients. He considered that this failure of cystine to follow its usual path of catabolism, in which the sulphur is excreted as sulphate sulphur in urine, is due to the inability of the liver to catabolize cystine normally in tuberculosis. He was unable to correlate the occurrence of cystinuria with the clinical condition since cystinuria was observed as frequently in the initial stages as in the advanced stages of tuberculosis. Although cystine crystals were never found in the urine, he was able to isolate the cystine from the urine by a relatively simple chemical procedure. He considered that this association of cystinuria with tuberculosis was of great significance in the study of the nutritive aspects of tuberculosis. In view of these findings of Monceaux, it has seemed of interest to us to report a similar study, the results of which are not in agreement with those of Monceaux.

We have examined the urines of about 150 tuberculous patients from the Tuberculosis Unit of the University of Michigan Hospital and from the William H. Maybury Sanatorium at Northville, Michigan. For the opportunity to study these patients, we are indebted to Dr. J. B. Barnwell of the University Hospital and Dr. Max Pinner of the Maybury Sanatorium. The clinical diagnoses of the cases studied included a considerable number of tuberculous conditions and various stages of the disease. Most of the cases from the Maybury Sanatorium were advanced pulmonary tuberculosis. The patients were receiving standard diets which included a considerable amount of protein. Twenty-four-hour specimens of urine were examined from the patients at the University Hospital. In the other cases the specimens were collected early in the day.

For the determination of the presence of cystine in the urine, three different procedures were used. In the earlier studies, the method of Looney (9) modified by the use of the more specific reagent of Folin and

Marenzi (10) was applied quantitatively. The Sullivan reaction (11) was used as a qualitative test as well as the modification of the cyanide-nitroprusside cystine test recently proposed by Brand (4). Of these tests the Sullivan test is probably the most specific as a test for cystine. In addition to these reactions attempts were made to isolate cystine from a number of the urines by the well-known Gaskell procedure (12).

Typical results with the application of the modified Looney method are presented in table 1. The control urines were collected from convales-

TABLE 1

Cystine content of urines of normal control and tuberculosis patients as determined by Looney method. All results are expressed as mgm. per 100 cc.

CONTROL	CYSTINE	TUBERCULOUS	CYSTINE
number	*mgm.*	*number*	*mgm.*
1	8.0	1 a	13.8 (11.4)
2	7.2	2 a	25.2* (21.0)
3	6.6	3 a	20.0 (16.2)
4	5.3	4 a	11.5
5	9.7	5 a	11.5
6	4.0	6 a	8.6
7	6.2	7 a	3.1
8	7.3	8 a	8.3
9	3.6	9 a	5.5
10	9.0	10 a	6.8
11	2.1	11 a	7.3
12	4.6	12 a	4.6

* The Brand and the Sullivan reactions for cystine were done on this urine and were negative.

cent patients in the orthopaedic wards or from workers in the laboratory. It will be seen that with possibly two exceptions (2a and 3a) the amount of cystine present in the urines of tuberculosis patients was within the range of variation of the normals. A repetition of the analyses on these patients three months later gave slightly lower values (represented in the table by the figures in parentheses). We do not consider these figures as significant, particularly as urine 2a was tested by the other and more specific tests used with negative results. The Looney method has been criticized frequently on the basis of lack of specificity. In the light of our experience we believe that cystine, if present, can be determined by this method, but that small variations from the normal figures are not to be accepted as significant unless the presence of cystine is confirmed by some other test.

In view of the failure to detect the presence of cystine in the tuberculous urines examined, it was felt that a more comprehensive study should be made on a larger number of urines, using the qualitative tests for cystine of Sullivan and of Brand. Of 57 tuberculous urines from the University Hospital, six gave doubtful reactions with Brand's test. Upon a subsequent examination of the urines of this same group three months later, three doubtful reactions were obtained. A second series of 75 urines from the Maybury Sanatorium was tested with uniformly negative results. In the entire group of one hundred and thirty-two, not one positive test by the Sullivan reaction was obtained. One urine only in this test gave a questionable reaction. In each case pure cystine solutions and urines to which cystine in small amounts had been added were tested as controls. The characteristic color was observed in each case where cystine was known to be present.

A number of these urines were also analyzed by the modified quantitative procedure of Looney (9) and gave results similar to those shown in table 1. As a final check on our results, twelve of the tuberculous urines of the second series were analyzed for cystine by the isolation procedure of Gaskell. No cystine was found in any of the samples examined.

It is difficult to explain the differences between our results and those of Monceaux. If, as stated by Monceaux, cystine occurs in appreciable amounts in 40 per cent of the tuberculous urines, it would seem that some positive tests would have been obtained in our total of about one hundred and fifty urines. Our failure to confirm the observations of Monceaux (8) is in harmony with the findings of Sylla (6), who was unable to observe cystinuria in any of the tuberculous patients studied in his clinic.

SUMMARY

1. Careful examination of the urine of about 150 tuberculosis patients has failed to demonstrate any relationship between tuberculosis and cystinuria as maintained by Monceaux.

2. The tests used (Sullivan, Brand, Looney, Gaskell) have been shown by control experiments to be sufficiently delicate to indicate the presence of cystine in small amounts.

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NONAPICAL INFILTRATIONS IN PULMONARY TUBERCULOSIS[1]

KARL FISCHEL[2]

The carrier problem in infectious diseases was first expounded in 1903 by Behring, when he pointed out that pulmonary tuberculosis in the adult is merely the final stage of an infection contracted in childhood. The so called onset of pulmonary tuberculosis is not the real beginning of the disease, but a revival, as Leon Bernard says.

The most extensive research work carried out since then has furnished us with considerable information as to the mode and time of tuberculous infections, while we know very little concerning the onset and development of the tuberculous disease. The uncertainties of its insidious beginning and its very vague subjective and objective symptoms do not permit an exact diagnosis, in spite of all the improvements in our methods of examination. Our efforts to detect the beginning of pulmonary tuberculosis remind us of the many unjustified convictions and acquittals based on circumstantial evidence.

The evolution of the anatomical lung lesion usually precedes the appearance of symptoms on which we can base our diagnosis of clinical disease, and we cannot hope to diagnose pulmonary tuberculosis in its very incipiency unless we search for the anatomical lesion even in the absence of physical signs. Furthermore, the intrapulmonary lesion is very often not followed at all by subjective or objective symptoms, for the innumerable autopsy reports describing scars in the lungs with a negative history leave no doubt that tuberculosis of the lungs can exist and heal without manifesting itself. Finally, our methods of physical examination are rather short-sighted and often the central parts of the lungs cannot be reached and explored by auscultation or percussion. The presence of a small, centrally located focus is consistent with negative physical findings and apparent good health, as we know since 1923,

[1] Comprising papers read before the Trudeau Society of Los Angeles, January 29, 1929, the Medical Staff of the Los Angeles General Hospital, February 25, 1929, and the Los Angeles County Medical Association, February 6, 1930.

[2] The Sanatorium of the Jewish Consumptive Relief Association, Duarte, California.

when an American writer, Wessler, in his text-book, *Diseases of the Chest*, described a heretofore unknown form of incipient pulmonary tuberculosis, which, on account of its vague symptoms and its fleeting character, had so long escaped detection.

Of the continental writers Assmann was the first to report isolated bronchopneumonic foci in the infraclavicular region in young adults. Soon many German writers described such infiltrations and the various changes which they may undergo, giving, on the basis of Ranke's theory, a logical and plausible interpretation of these lesions. The heated discussion which followed these reports led in Germany, at least, to a revision of the time-honored doctrine of the apical origin of pulmonary tuberculosis. The so called new teachings did not advance suddenly and abruptly, but on the basis of painstaking and systematic investigations over many years. Elaborated step by step by Franz Redeker and his many coworkers, they are at present accepted virtually by the most experienced German clinicians; while Loeschke, Huebschmann and other pathologists lead the opposition. The work of Franz Redeker, who for the past seven years has been the dominant power in the revolution threatening to shatter the old dogma of the apical origin of phthisis, will be fully discussed later. The merit of having reopened the problem of phthisiogenesis belongs undoubtedly to him, and the importance of nonapical infiltrations, as the first manifestation to which the development of the various forms of acute or chronic pulmonary tuberculosis can be traced, cannot very well be discussed without mentioning his name.

In striking contrast to the feverish interest which the German writers took in the infraclavicular infiltrate the English authors remained at first indifferent. Wessler's classic description had been ignored, and Fishberg, who reported 11 cases in 1928, was the first American writer to discuss the importance of infiltrative processes in the development of pulmonary tuberculosis. His conclusions agree with the newer views in all essential points. The next publication dealing with this subject came from the Detroit Municipal Sanatorium, Northville, Michigan. The writers, Douglas, Pinner and Wolepor, give a short abstract of the German literature, and differentiate on the basis of clinical, radiological and statistical data between subapical infiltrative and nodular apical tuberculosis as two different clinical entities, demonstrating the rôle which each type plays in the development of progressive tuberculosis. Douglas and Pinner, in their second paper, discuss more fully the pathogenesis, pathology, and clinical diagnosis of acute subapical infiltration,

and show several developments of its pathology by X-ray plates. The writer himself has reported a number of cases in several papers, and has emphasized the importance of nonapical infiltrations from the standpoint of treatment and prevention. Recently Fishberg and Shamaskin have presented statistical evidence demonstrating the benign course of apical tuberculosis in contradistinction to the grave significance which infraclavicular lesions have in the development of active and progressive disease, by correlating the clinical histories and roentgenographs in 1000 cases over a period of five years. Their report shows that, while in the infraclavicular group only 1.8 per cent have survived, in the apical group 31.7 per cent were alive ten or more years after the first appearance of symptoms. It will be seen that the few American writers who are dealing with the subject have recognized the significance of these newer teachings.

It is of interest to note the unmistakable similarity of the older French viewpoint with the newer German concepts, even though their terminology is entirely different. The French school has known for more than sixty years of the *congestion pulmonaire* appearing not only in respiratory infections but also in pulmonary tuberculosis. French observers then described certain forms of apical tuberculosis of an undoubtedly benign character and separated these forms from other more malignant types which are localized in the lower half of the upper lobe and which quite often involve the interlobar fissures (*pericissuritis*). The acute exacerbations, for which the German writers use the term *Schub*, which is best expressed by the word *wave*, is also spoken of in the French literature (Bezançon's *poussee-evolutive*). The dissemination by aspiration which Redeker calls *aspiration Aussaat* reminds us of the *granulies discretes* of Bard and Piery, while the hypothesis of the nonapical development of phthisis finds its expression in the *zones d'alarme* of noted French writers (Piery, Sergent, St. Chavet and others). All these observations, however, could not shatter the old doctrine of the apical origin because the work of Ranke, who had the vision to recognize certain fundamental laws in the course of the disease, from the first infection to the final stage, had not as yet been known.

RANKE'S THEORY[3]

Ranke's three-stage classification has been hailed with enthusiasm by many and assailed and criticized by others. It is now accepted with

[3] The following presentation is based on Redeker's work as expounded in his two textbooks and numerous papers.

important modifications by Redeker and his school and by many leading clinicians. While Aschoff essentially agrees with his concepts of tuberculosis, many other pathologists still reject it. Incidentally it may be mentioned in this connection that Ranke, although known as a pathologist, conceived and developed his theory during his years of dispensary work, as he states in a letter to Pagel (quoted from Redeker). Ranke as a pathologist, who sees the final results only, and who tries to reconstruct the development by retrospection, tried in vain to solve those problems to which clinical observations had attracted his attention, as, for instance: Why does the first infection invariably lead to the marked involvement of the lymph nodes which is never observed in the isolated tertiary phthisis? Or, why does pulmonary tuberculosis very often run an afebrile course in an advanced case, while acute and general symptoms are quite common during an earlier stage of the disease?

Another vital question as to why, in one case, exudation predominates and in another proliferation, was raised by the introduction of the Fraenkel-Albrecht classification, which distinguished the exudative, proliferative and fibrotic forms. These and similar questions Ranke tried to answer by his theory. Ranke's ingenious conception explains these puzzling phenomena by correlating the immunobiological reaction with the pathomorphological process. Robert Koch already had suggested the solution by showing in his classical experiment that the reaction to the first infection is proliferative, whereas the anatomical response to superinfection is inflammatory, or, as Krause has put it, "Proliferation is the essence of native tissue response, exudation is the essence of allergic response." After the discovery by Pirquet of the skin reaction, the changes in the tissue reaction to bacilli and bacilloproteins attracted much more attention than the difference in the pathologico-anatomical process which Koch had described so clearly. It was left to Ranke to recognize that the immunobiological reaction and the pathomorphological process are inseparably linked together and influence each other to such an extent that it is impossible to state whether the anatomical process induces the corresponding phase of immunity, or *vice versa*. Or, in other words, whatever changes take place in and around the focus, the anatomical manifestation of the phase of immunity and the degree of allergy is the immunobiological expression of the pathomorphological process.

Ranke distinguishes three stages in tuberculosis as in all infectious diseases, each one characterized by a different phase of immunity with

different modes of propagation of the infection. Ranke's first stage, that of the primary complex, comprising the site of the first infection and the regional lymph nodes, is marked by a profound modification of all tissue cells developing after the first inoculation (known since Pirquet as *allergy*). The defense of the body against the first invading bacilli is markedly nonspecific, and consists of mechanical defensive measures such as are called into play against any irritating foreign body. To quote Krause, "The body treats the first bacilli as it would any foreign body, that is, it walls them off with tubercles and sets them apart from normal tissue." Krause also calls attention to the fact that the acid-fast tubercle bacillus is highly irritating and most probably responsible for the nodular tubercle. The highly irritating lipins contained in the envelope of the acid-fast bacterium may explain the insidious course of the first infection in tuberculosis, which is in striking contrast to the acuity of symptoms caused by the onset of other infections of the respiratory tract. Since the tubercle is avascular, the infection can be propagated mainly by the lymph-vessels. Tuberculosis at this initial stage is therefore predominantly a tuberculous lymphadenitis and the infecting bacilli are walled off within the lymphatics, from which they cannot escape unless the mechanical barrier is broken through, as, for instance, when a caseated lymph node breaks into a blood-vessel, or into the bronchial tree.

Ranke's second stage begins with the first reinoculation of the allergic animal body. All tissue cells have become sensitized to the infecting bacilli and their proteins. The tissue response is then prompt and intense, causing local and general allergic symptoms. Inflammatory changes, consisting of hyperaemia, oedema, emigration of lymphocytes, etc., make up the anatomical picture of the focus of reinfection. General symptoms may, or may not, be present, depending on the size of the focus and the degree of perifocal inflammation. During this stage the infection spreads mainly through the blood-stream, although all other ways are open for propagation. Ranke's second stage, that of generalized tuberculosis, is therefore characterized by hypersensitiveness to reinfecting bacilli and bacilloproteins, by inflammatory tissue changes, and by distant haematogenous metastases.

The third stage, that of isolated organ involvement, is distinguished by a relative anergy and by intracanalicular propagation. The disease spreads by continuity or through the visceral ducts of the body.

Ranke's three-stage system does not run parallel with any other classification, and has therefore been widely misinterpreted. It refers,

not to the extent of the lesion, but to activity and quiescence and to retrogression and progression. Phthisis can develop at any of the three stages, and it would be a mistake to identify the tuberculosis of the child with the second stage, or to designate the chronic tuberculosis of the adult arbitrarily as tertiary phthisis. The acute caseous pneumonia of the infant is, for instance, a prototype of the first stage. The tuberculous bronchopneumonia of the child or adult, which leads to meningitis, is an example of the second stage with its frequent distant metastases; while the third stage is exemplified by the chronic forms of tuberculosis of the adult. While in the latter case the three phases of allergy follow each other in the order, allergy, hypersensitiveness, comparative anergy and finally exhaustion anergy, the infant that dies from caseous pneumonia or meningitis never reaches the third stage.

Ranke's teachings were criticized from many angles. The objections, however, affect only details, and even Ranke's opponents recognize the breadth of his vision. His conception is only a working hypothesis which was never meant for practical application in single cases, but offers a concise explanation of the evolution of tuberculous infections independent of the age of the subject but in relation to the age of the infection. This point is illustrated by a recent observation by Blumenberg, who described a fresh primary focus in a man 71 years of age, which presented the same structural changes as those described by Ghon and others in children.

The weak points of Ranke's theory have been admitted by his most enthusiastic adherents, with important modifications which must be considered as essential elements of the recent views. Ranke originally distinguished only two distinct forms of reaction, that of hypersensitiveness and that of immunity. Later, he introduced, as the first stage, that of infection and prodromal symptoms with an altered reaction to bacilloproteins which he called *sclerotizing allergy*, a term that apparently has reference to the indurative changes which characterize the primary focus. While the first stage is anatomically well defined, no such sharp borderline can be drawn for the immunobiological reaction characterizing the second phase. And, again, the significance of the comparative anergy of the third stage is likewise not sufficiently clear. This anergy may either mean the exhaustion anergy which we so frequently observe in far-advanced cases when immunity has broken down and the tissue cells have lost their capacity to respond to reinfection with inflammatory reactions, or it may mean the comparative anergy of quiescent cases when

the stormy allergic symptoms have subsided. Ranke has, of course, reference to the latter anergy, at which stage the comparative immunity which has been developed is strong enough to prevent the formation of new foci, even if bacilli may circulate in the humoral pathways.

The third stage is, according to Ranke, the last and final phase, and in his opinion a return to the second or to the primary stage of allergy is not possible. His three-stage classification is therefore too rigid, and fails to explain the cyclic course of tuberculosis. Any reactivation would, as Pagel has pointed out, induce a fourth stage in analogy to the second, which again would necessitate a fifth and sixth stage, etc. Redeker most emphatically disagrees on this point with Ranke, and asserts that in the development of tuberculosis recurrent changes occur between the secondary and tertiary allergy. The order in which the three stages follow each other from the first infection to death, or cure, is reversible as to time; and a return to a preceding phase, particularly from the third to the second phase, is quite common. While, on the whole during the course of the disease, the tendency prevails to reach allergy three, after the first two stages the majority of cases show alternating periods of hypersensitiveness and comparative anergy, corresponding to alternating periods of activity and quiescence. Thus, when a cure is effected, the stage of allergy one is definitely reëstablished; and in exceptional cases the complete anergy, which existed before the contact with the tubercle bacilli, can be obtained again as proved by negative skin reaction.

It is obvious that Ranke's second stage represents the critical period in the life of the patient and that the duration and the degree of allergy decide his fate. He cannot recover unless he overcomes the phase of hypersensitiveness, thus stabilizing his immunity. The more allergic the body is, the more intense will be the anatomical reaction, and the more will exudation and perifocal inflammation predominate in the anatomical picture. Lesser degrees of allergy will go hand in hand with less or no exudation and a mild perivascular or peribronchial inflammation. Furthermore, absorption of exudates and productive-indurative changes will manifest themselves by subsiding allergic symptoms. It will be seen that all factors which tend to increase the reactibility of the body must be considered unfavorable. Redeker and his coworkers claim that the appearance, duration and intensity of the phase of the second allergy depend, therefore, not only on the virulence and the dose of the reinfecting bacilli, but to a great extent on nonspecific factors. Under this heading may be grouped intercurrent diseases, such as whooping-cough,

measles, pneumonia and other respiratory infections, as well as the age factor, pregnancy, trauma, the constitutional makeup of the individual and the influence of the endocrine and autonomic nervous systems. On the basis of Ranke's conception, with the modification just described, Redeker in 1927 formulated several fundamental laws which underlie the development in the course of the disease, of which the following may be mentioned:

1: With preëxisting pulmonary tuberculosis, no matter of what stage, the formation of a new intrapulmonary focus cannot take place without local or general allergic symptoms.
2: The formation of a new focus is always accompanied by allergy two, although in exceptional cases the allergic symptoms may be so mild or of such short duration, that they are not noticeable. Tertiary phthisis (in the sense of Ranke) is therefore not a new formation but a transformation of a secondary phthisis.
3: Exudative and proliferative phthisis are not principally two different types of pulmonary tuberculosis, but the anatomical manifestations of two different allergic phases.
4: There is not any difference between pulmonary tuberculosis of the child and that of the adult.

According to Redeker, the life of a patient suffering from pulmonary tuberculosis consists therefore of a number of cycles with alternate periods of allergy two and three. Each cycle begins with a reinfection, leading to the formation of a new focus, and causing allergic symptoms, and is terminated by productive-indurative tissue changes and the simultaneous reappearance of comparative anergy. Gradually more and more parts of the lungs become involved until the stage of exhaustion anergy is reached. It is of significance to note that Ranke's conception of the inflammatory character of all new foci is at present admitted by leading pathologists. Aschoff, Huebschmann, and other pathologists agree that all foci of reinfection begin with an exudative phase, which, as explained above, is characteristic for Ranke's allergic stage.

THE EARLY INFILTRATE

Into the discussion of Ranke's work, the discovery of isolated bronchopneumonic foci, by Assmann, fell like a bombshell. On the basis of Ranke's conception, the development of infiltrations with perifocal inflammation, following reinfection, could have been foreseen. Thus,

if Ranke was correct, the new focus due to reinfection must of necessity be inflammatory in character, and could be localized in any portion of the lung, to which the reinfecting bacilli could be brought, either by the inhaled air, or carried by the lymph or blood-stream from any deposits in the intrathoracic lymph nodes or older intrapulmonary lesions. The opening shot against the classical teachings was fired by Brauening, who, in 1924, reported that of 76 cases of apical tuberculosis only 2.6 per cent had progressed to open tuberculosis after 3 years, and only 7 per cent after 7 years. He further showed that of 248 patients with positive sputum only 13 per cent gave a history of apical tuberculosis. This report brought out the puzzling fact that the percentage of progression from apical lesions to open tuberculosis was lower than the entire calculated mortality from tuberculosis. Similar evidence was presented by Lydtin and Romberg, Redeker and Walter and Kayser-Peterson. At this time, Assmann had published the first description of isolated infraclavicular infiltrations. This new form of incipient tuberculosis was at once studied and discussed by a number of observers, among whom were Assmann, Redeker, Ickert, Grass, Romberg, Klemperer, Ulrici, Lydtin, Bacmeister, Frischbier, Haudek, Fleishner and others. During the years 1924–1926 the new doctrine was elaborated upon by Redeker and his coworkers. In 1928, at the German Tuberculosis Convention in Wildbad, it was discussed and accepted by the majority of the German clinicians. Redeker, as the medical head of the big steelworks at Muelheim, carried out systematic physical and serial X-ray examinations for a closed group of a hardworking population. During the years from 1920 to 1926, on the basis of his findings, he traced the origin and development of the various forms of acute and chronic pulmonary tuberculosis to nonapical infiltrations. According to Redeker and his followers, the infraclavicular infiltrate, which will be described presently, is the first focus of reinfection.

It is the contention of the new German school that pulmonary tuberculosis nearly always begins with a bronchopneumonic focus in some part of the lung below the clavicle, from where it spreads by the formation of new foci to the middle field and the base, involving the apices at a much later period. While late apical tuberculosis is quite common, incipient apical tuberculosis is extremely rare. Our diagnosis of incipient tuberculosis, localized in the apical region, is therefore, in reality a false late diagnosis, and our treatment, not early, but delayed therapy. Furthermore, apical tuberculosis is nearly always benign and rarely progresses to

destructive disease. Thus the patient with the well-known changes in his apical region, which have been interpreted as evidence of incipient tuberculosis, is not in need of any care, unless he shows symptoms of activity, because these changes are always secondary and of no significance.

The salient features of the newer teachings are, therefore, the overwhelmingly important rôle which the allergic focus and perifocal inflammation play in the development of progressive tuberculosis of the adult, and on the other hand the minor, almost negligible, part in the pathogenesis which is attributed to changes in the apices. The early or incipient infiltrate is usually found in the region below the clavicle, toward the periphery and nearer to the dorsal surface of the lungs. The characteristic feature is not their localization but their bronchopneumonic structure. In a study of 117 early infiltrates Redeker reported the localization as being infraclavicular in 58 cases, middle field in 38, lower field in 15, subclavicular in 4 and apical in 2 cases. They are described as soft, cloudy, homogeneous shadows, the size of a cherry to that of a plum, surrounded by normal lung tissue. The physical symptoms are usually very indefinite or entirely lacking. At times only a slight impairment of resonance and diminished breath-sounds over a circumscribed area can be elicited. The subjective symptoms are equally insignificant and irregular. In many cases the patients have no complaints at all, or may have vague symptoms, or a slight subfebrile temperature; or a sudden haemorrhage may bring the patient to the dispensary or office. Very often a history of a cold or of a grippe of a short duration is given. German writers mention, besides the moderate rise in temperature, an increased sedimentation to 12 and 18 mm., and changes in the white blood picture, as objective symptoms. A slight shift to the left, and a moderate increase in the speed of sedimentation, are of differential diagnostic significance, and point to tuberculosis, whereas a marked acceleration of sedimentation and a strong left shift speak for other respiratory infections. The onset of the early infiltrate is usually so insidious, and the subjective and objective symptoms so unobtrusive, that a diagnosis without fluoroscopy and good stereoscopic films is hardly possible. Redeker states, "It is necessary to search for the early infiltrate, whereas the apical lesion forces itself upon the observer." The early infiltrate is anatomically a tuberculous bronchopneumonia in a small circumscribed area. Both Assmann and Schmincke had occasion to perform an autopsy, where during life an X-ray diagnosis of an early

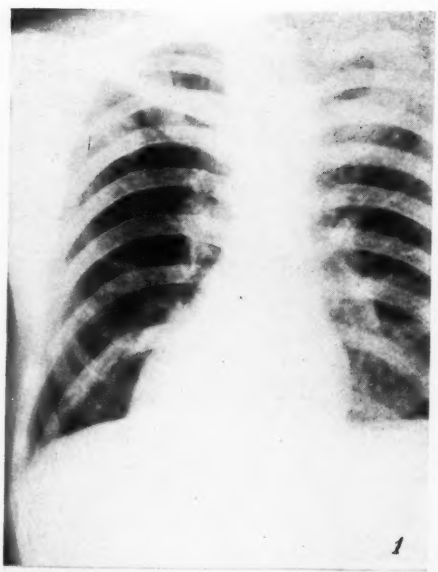
infiltrate had been made, and found a centrally caseated focus, surrounded by perifocal inflammation, with a few disseminated small foci in its neighborhood. Pagel reported another case, and a fourth case which had not as yet been published came under the observation of Ghon and Kudlich (quoted from Redeker). This last case is particularly interesting because Ghon and Kudlich found an acute infiltration with a caseated centre, while the apices, which were examined microscopically and by serial sections, were found to be absolutely free. Figure 1 gives an example of an early infiltrate in the stage of beginning fibrosis. The case was as follows:

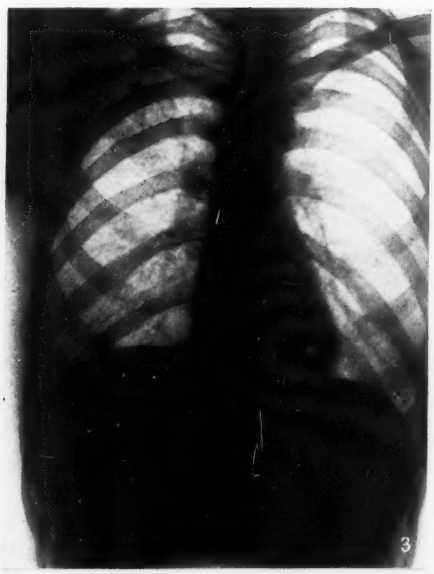
KW., 33 years old, admitted to Los Angeles General Hospital, O.P. Dept. No complaints pointing to chest. Chest findings negative. Dense oval area of infiltration in the left upper lobe posteriorly, rather sharply circumscribed and with no surrounding inflammation.

The early infiltrate may undergo various changes, the most favorable development of which is complete spontaneous retrogression. The infiltration and exudation may be absorbed, leaving no trace. More often, indurative changes set in and organization takes place with subsequent calcification, thus reserving on later films a very dense, sharply outlined shadow at the side of the early infiltrate.

A later stage of fibrosis and organization is exemplified by figure 2, which shows fibrosed infiltrate in the right subclavicular region.

The developments of the early infiltrate which lead to the acute forms of phthisis are manifold, and sometimes of a dramatic suddenness. We are dealing with a tuberculous bronchopneumonia, which is surrounded by an area of perifocal inflammation, and in no way walled off from the surrounding tissue. Because it has this free communication through the bronchi, blood-vessels and lymphatics to other parts of the lungs, any development is possible. The first crises arise as an infiltrate progresses to caseation, softening and cavity-formation. At the stage of caseation, an irregularly outlined kernel of deeper density can be made out on the film, which corresponds to the beginning demarcation of the caseated centre. Even at that period the caseated focus can undergo induration. The stage of caseation is marked by increased allergic symptoms. The patient appears decidedly toxic, his temperature rises higher than that in the initial stage, his pulse is rapid, and he gives the impression of being acutely shocked. The formation of small round cavities is frequently found on the very first film and may help to





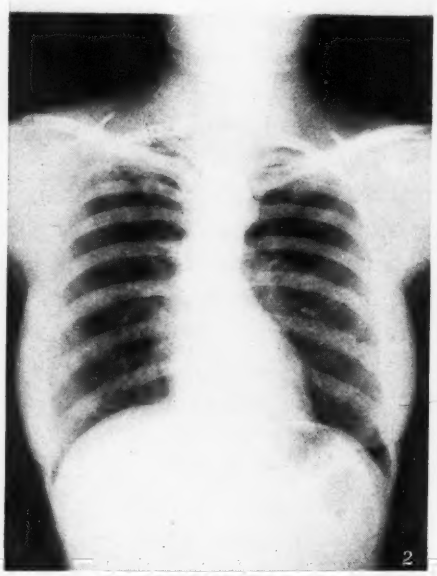


FIG. 1. See text, p. 149.

FIG. 2. See text, p. 149.

FIG. 3. X-ray, showing area of infiltration in right upper lobe. Its densest portion is in the infraclavicular region. Right interlobar septum thickened.

FIG. 4. X-ray, showing complete collapse of the right lung and obliteration of cavity.

differentiate these tuberculous lesions from infiltrates of other origin. The subjective and objective symptoms at this stage are altogether out of proportion to the insignificant physical findings. If the perifocal inflammation reaches the pleura, the patient may complain of pain and of a dry cough, whereas, if the softening and cavity-formation take place, the patient usually begins to cough and expectorate. The fate of the patient at this critical period depends on the stabilization of his immunity. Marked allergy will cause an extensive perifocal inflammation, which again will tend to accentuate the existing hypersensitiveness. One toxic shock follows another. The inflammation and perifocal inflammation rapidly extend until the greater part of the whole side is involved. Thus we get the well known clinical picture of acute caseous lobar pneumonia or caseous bronchopneumonia.

It is the contention of the German writers that this malignant development can be prevented if the early infiltrate is diagnosed, and proper treatment instituted in time.

The following cases came under our observation in the stage of beginning caseation:

BW., white female, 19 years old, milliner. Personal and family history negative. Three weeks ago caught a cold. Since then complains of lassitude. *November 2, 1928:* Had sudden haemorrhage; sent to hospital; breath-sounds on right side diminished, otherwise negative; temperature 98 to 102, pulse 90–136; sputum negative. Under rest and treatment the haemorrhage stopped after two days. *November 8, 1928:* Artificial pneumothorax induced, 400 cc. given; temperature dropped sharply to normal and remained normal since then. *December 1, 1930:* Patient has gained 25 lbs. (See figures 3 and 4.)

A similar case is the following:

GE., 18 years, family and personal history negative; influenza October, 1929; sore throat. *October 13, 1929:* Sudden haemorrhage; admitted to hospital; physical findings negative; temperature 102 to 103. The next picture, taken the very next day, shows already a markedly increased area of infiltration (figures 5 and 6). Pneumothorax was induced October 17, 1929 (figure 7). The right side was well compressed. The patient has gained 13 lbs. and is free from all symptoms.

The next case will serve to illustrate the tendency to rapid extension which is characteristic of the early infiltrate:

DL., 38 years, housewife, Negress, admitted to General Hospital February 13, 1929. Family and personal history negative. Four pulmonary haemorrhages

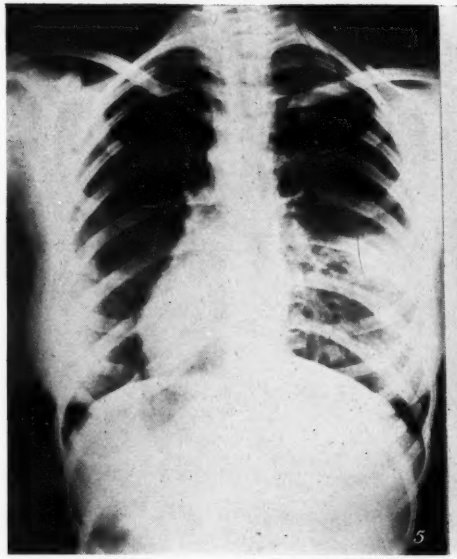


FIG. 5. (October 14, 1929.) Area of infiltration in the right middle field near the periphery, with a definite round cavity.

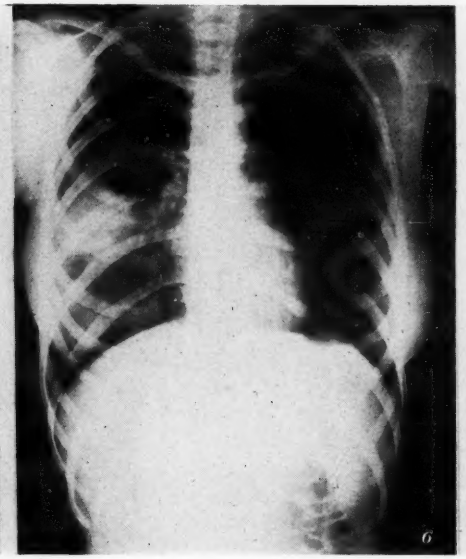


FIG. 6. See text, p. 151.

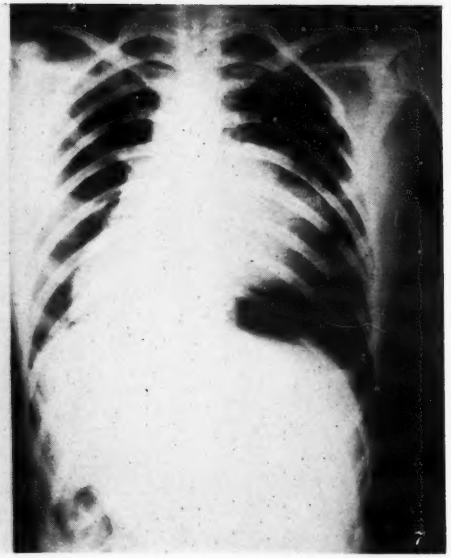


FIG. 7. See Text, p. 151.

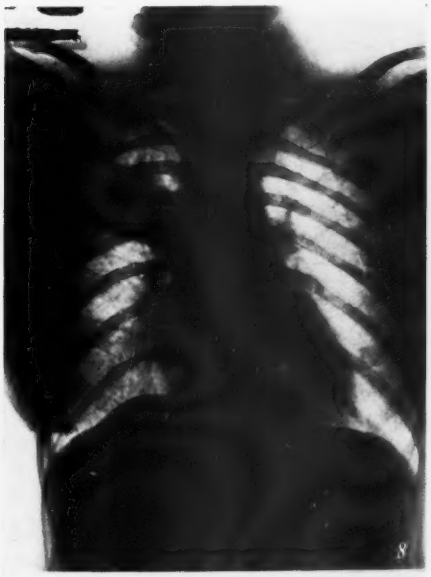


FIG. 8. Hazy infiltration in the right upper lobe just above and extending to the interlobar fissure. Apices clear.

FIG. 9. See text, p. 155.

FIG. 12. See text, p. 155.

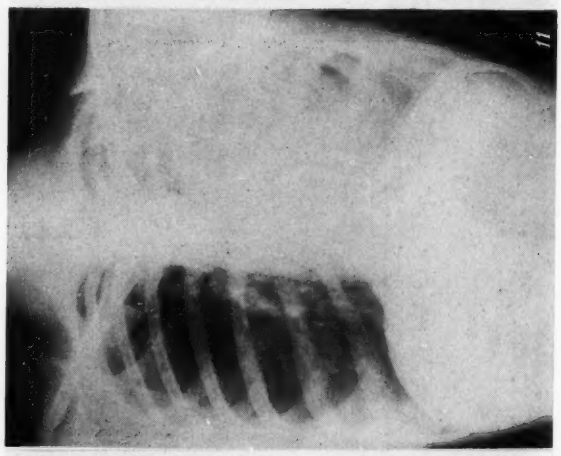


FIG. 11. See text, p. 155.

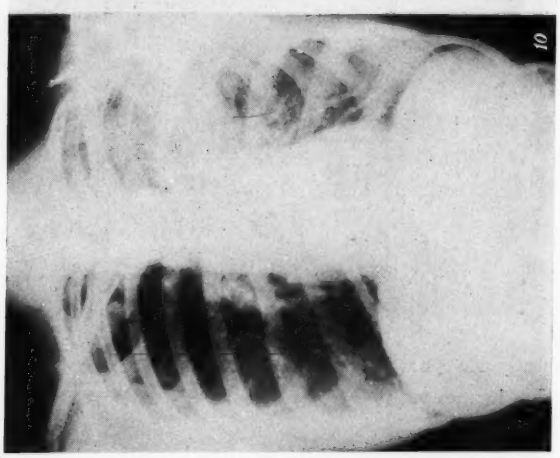


FIG. 10. See text, p. 155.

on day of admission. Influenza one week ago; since then cough and fatigue. Temperature 99.6°; impaired resonance over right upper lobe with diminished breath-sounds; sputum positive (figure 8). Artificial pneumothorax was considered, but before it could be induced another picture was taken which showed a rapidly extending infiltration, involving the lung from the clavicle to the base. Pneumothorax was tried but was unsuccessful due to adhesions which had developed (figure 9).

A similar rapid progression could be observed in the following case:

EG., admitted November 20, 1929; took sick October 17, 1929, with an acute attack of influenza. The first film (figure 10), taken October 28, showed an

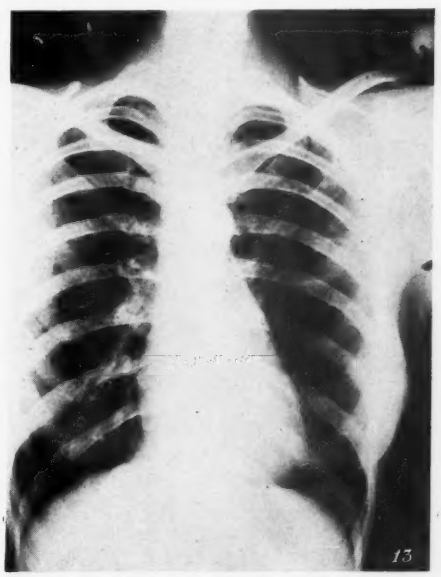


FIG. 13. See text, p. 156.

infiltration in the lower portion of the left upper lobe. The patient was kept under strict bed-rest. A picture (figure 11), taken November 12, 1929, showed an involvement of almost the entire left side, with faintly mottled areas in the right upper lobe. Two days after admission to J. C. R. A. Sanatorium pneumothorax was instituted. The patient is afebrile, has gained 15 lbs. in weight, and has an almost complete compression of the left side.

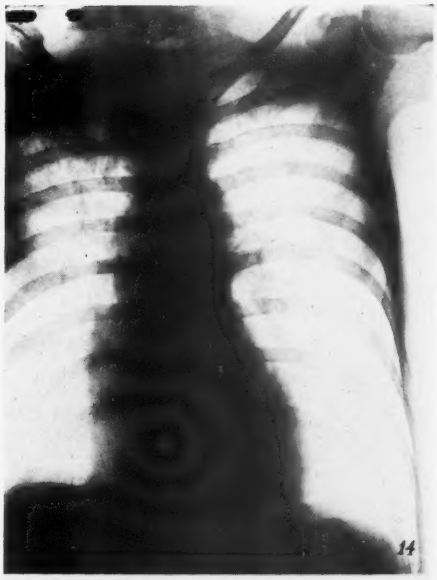
These cases illustrate the necessity of applying artificial pneumothorax in the treatment of infiltrations, if the allergic symptoms persist, and if

the tendency to spontaneous retrogression does not become manifest within a short time. By this simple surgical measure, we not only prevent the development of an acute progression, but will also frequently save the patient from a long chronic disease and years of sickness. Compression by surgical means at the stage of caseation or extension can be compared in its effect to an appendicectomy before rupture of the appendix. Artificial pneumothorax is a harmless and simple measure by which we can localize the infection, which otherwise frequently spreads rapidly under conservative treatment. Hyperallergic symptoms, however, very often subside without surgical interference. At the same time resorption takes place and indurative changes set in, leaving areas of fibrosis at the site of the infiltration. Redeker uses the term, "fields of induration," for these fibrotic areas, an example of which is given in figure 13, a film taken of the chest of

MA., 24 years, nurse. One year ago active tuberculosis with positive sputum, and showing an area of fibrosis below the left clavicle.

The most critical period in the development of the early infiltrate is reached with the formation of the round, nonencapsulated cavity, which Ulrici has compared to a volcano, because the infection may now spread to the bronchial tree. According to Redeker, the dissemination, which is always accompanied by marked allergic symptoms, is bronchogenic and not haematogenic. Haematogenous metastases, which are common occurrences in children, are, as a rule, irregularly distributed, and cause only mild symptoms or none at all. On the other hand, the typical dissemination by aspiration never appears in both lungs, and is first noticeable in the lower region of the affected side in the area between infiltrate and hilum. It is manifested on the X-ray film by an increased cloudiness in the neighborhood of the infiltrate. In the hazy area there soon appear soft, oval shadows, which never resemble the well-known clover-leaf spots characteristic of the fully developed acinonodular tubercle. Redeker interprets these shadows as areas of perifocal inflammation around minute new foci. These spots disappear in a surprisingly short time, often with the absorption of the exudate, or else show retrogressive changes, leaving a hazy network of fine fibrous strands with a few disseminated soft shadows.

At any time during the development of an early infiltrate, a bronchogenic propagation may lead, accompanied by secondary allergic symptoms, to the formation of another infiltrate. Because of its similarity



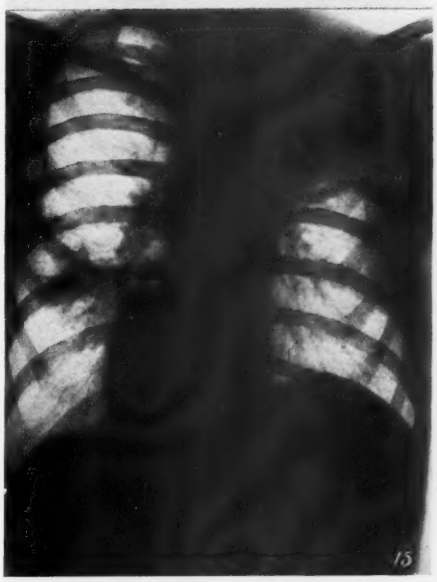


FIG. 14. See text, p. 158.
FIG. 15. See text, p. 158.

in origin, structure and development to the early infiltrate, Redeker uses the term "daughter infiltrate." These may appear suddenly in heretofore healthy parts of the lungs, and very often in the contralateral lung.

The sites of predilection of new bronchopneumonic foci of bronchogenic origin are, according to Fleischner (which he compares to "bronchial infarcts"), the base of the upper lobe, particularly in the axillary region, and the dorsal medial portion of the middle lobe on the right side, and the dorsal portion and base of the upper lobe on the left side.

Figures 14 and 15 are self-explanatory, and show a "daughter infiltrate," with a small cavity in the contralateral lung.

The allergic infiltrative phase, with which all new foci begin, makes it necessary to distinguish various types of infiltrations which may appear in the course of the tuberculous infection. Thus acute inflammations, which differ in no essential way from initial infiltrations, may form around old foci in the lungs or in the hilar lymph nodes. The clinical picture and prognosis in late infiltrations are determined, not by the site or the size of the old lesion, but by the degree and the extension of the perifocal inflammation. Inflammatory infiltrations around old foci are distinguished by their greater tendency to retrogression, and a progressive development is comparatively rare. For this reason, a differentiation of the various infiltrative processes may be of practical value.

In Redeker's terminology we have to distinguish:

1: The primary infiltrations around the primary focus. To this group belong the acute forms of phthisis in babies, who die in a very short time without ever giving a positive skin reaction. Also the numerous cases of acute tuberculosis of the lungs observed among native troops during the war. In these cases the first contact with the tuberculous infection led, without the usual intervening period of latency, to a very acute and progressive tuberculosis.

2: Secondary infiltrations, that is, perifocal inflammations around old quiescent, more or less labile foci. Redeker speaks of a "perihilar infiltration" if the focus is a tuberculous intrathoracic lymph node, and of a "lung infiltration" if the focus is an old intrapulmonary lesion. Perihilar infiltrations are rare in adults, but quite common in infants. These forms have been described by various writers, such as Sluka, Eliasberg and Neuland. Instances of secondary infiltrations in the adult are the focal reactions following an overdose of tuberculin, or overexposure to sun and X-rays, strenuous exercise, intercurrent diseases, etc.

3: Early infiltrations, which Redeker defines as intrapulmonary inflammatory

infiltrations, due to the formation of a new focus in a heretofore unaffected portion of the lung.

4: Late infiltrations in parts of the lungs already affected.

A perihilar infiltration in an adult is shown in figure 16. The patient, a young girl of 23, had also a large infiltration in the lower lung field of the same side, for which artificial pneumothorax was instituted with good results.

Figures 17 and 18 give an example of a secondary infiltration following an acute pleurisy. A comparison of the two films will demonstrate the

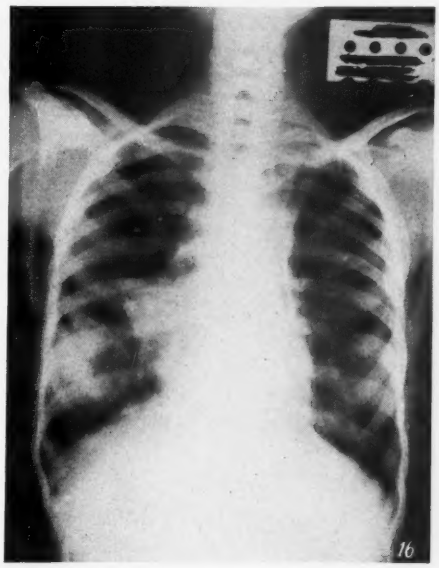


FIG. 16. See text, p. 159.

perifocal inflammation around obsolete foci in both apices, which was absorbed rapidly, leaving the same hard shadows seen on the first film.

APICAL TUBERCULOSIS

Redeker and his followers, while not denying the possibilities of phthisical development from apical tuberculosis, claim that the significance of apical lesions as a forerunner of progressive disease has been grossly overestimated. In attacking the old theory, Redeker does not mince words. He points out that the classic theory of apical origin is based on

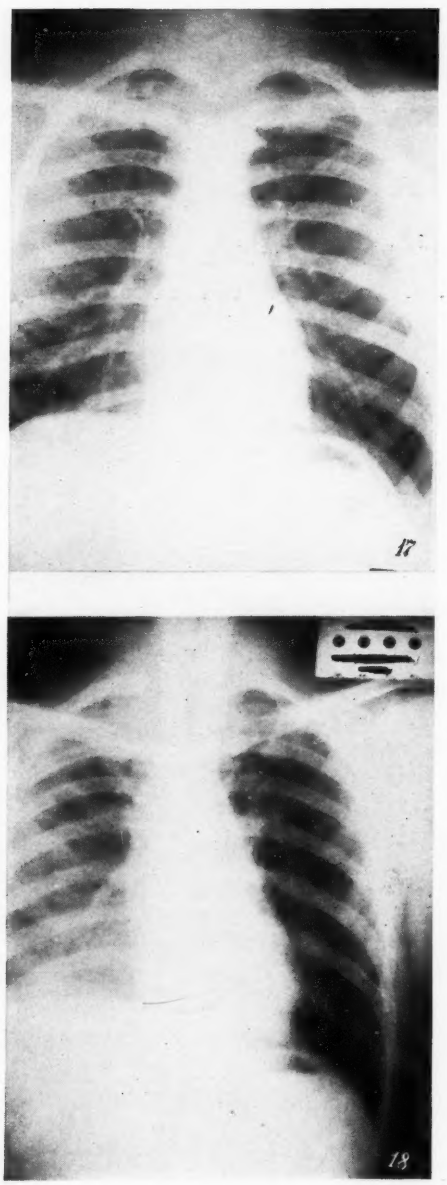


FIG. 17. February 7, 1927
FIG. 18. April 14, 1930

a series of false conclusions. After the discovery of the tubercle bacillus by Robert Koch, attempts were made by clinicians to diagnose the prebacillary stage of phthisis. The fact that changes in other parts of the lungs seemed to be almost invariably preceded by positive findings at the apices, likewise innumerable necropsy reports revealing pathological processes of apparently long standing in the apical region, whenever tuberculosis involving other parts of the respiratory organ was present, and even in the absence of a history of active tuberculosis during life, seemed to prove conclusively that the apices were the site of predilection from which pulmonary tuberculosis first develops and begins its disastrous course toward the base. The doctrine that pulmonary tuberculosis in the adult begins at the apex, though not supported by animal experimentation, was so firmly established, that radiography at first was welcomed as a new method to furnish additional evidence, and not as a means of critical reinvestigation of the prevailing theory. The discrepancy between physical findings and X-ray reports started a contest between refined and overrefined methods of physical exploration and interpretation of shadows in the apical fields, with the result that slight changes in the note of percussion, or in the character of the breath-sounds on the one side, and suspicious shadows on the films on the other hand, were considered as evidence of apical tuberculosis. Finally the missing link in the chain of false conclusions was found in the therapeutic proof. For the good results obtained by institutional treatment in lesions, the initial character and tuberculous origin of which had to be proved but was taken for granted, seemed to prove that we were dealing with the initial stage of pulmonary tuberculosis, because this treatment apparently prevented the development of progressive tuberculosis.

The consensus of all recognized text-books is that the adult type of pulmonary tuberculosis is prevailingly apical even though the primary infection is contracted during childhood. According to the generally accepted views, chronic pulmonary tuberculosis develops from the apex with miliary tubercles, although none of the theories, which have been advanced, can account for its predisposition. The road from the minute apical focus led in an apparently unbroken line, subject, of course, to exacerbations and remissions, by a slow and gradual extension to the involvement of the apical field, and from there to the moderately advanced and finally to the far-advanced stage. All current classifications are based on the slow evolution and gradual extension, which is now emphatically rejected by the newer German school. Apical tuberculosis charac-

terized by the well-known syndrome of slight changes in the note of percussion, and the character of the breath-sounds with or without fine râles, is, according to Redeker and his followers, not the beginning of pulmonary tuberculosis, but the late result of a benign form of development. The cause of these insignificant and secondary changes is an ascending inflammation, while a descending extension is extremely rare. The traditional physical and X-ray findings are easily explained by the fact that any lesion in the subclavicular region will tend to diminish the elasticity of the lung situated above, and that scar-formation may often interfere with the proper aeration of the apices. Likewise, an ascending apical pleurisy may cause changes in the breath-sounds, and give a gray appearance to the apical field. The proper interpretation of changes in the apices must take into consideration two facts which have been confirmed by many observations and which are emphasized by Redeker and his coworkers: one, that retrogression in the apex is, as a rule, much slower and less complete than in any other parts of the lung field, and that changes may persist long after the lesion below the clavicle or in the middle field has disappeared. The difference in the speed and degree of complete resolution, which can be observed in lesions above and below the clavicle, is demonstrated by the following case:

JP., 43 years, admitted to Sanatorium August 11, 1929. Physical examination revealed the presence of an inactive fibrotic lesion in the upper half of the right upper lobe. This impression was confirmed by the film, figure 20, which showed heavy mottling above the second rib, and a dense opacity above the clavicle. Anyone, looking at this film, would be convinced that the oldest lesion is situated in the right apex, whence it extended downward. A film taken in an eastern sanatorium the year before gave an entirely different aspect to the case, for it showed that the infection had in reality spread toward the apex, and that our film showed the fibrotic residues of inflammation in the middle field below the clavicle, which had undergone resolution (figures 19 and 20).

The second fact, of which a good example is given in Douglas and Pinner's article, is the apparent migration of cavities and other structures toward the apex. Atelectatic or cirrhotic tissue changes in the apex tend to displace by traction lesions which are localized below the clavicle or in the middle field toward the apex. The projection toward and above the clavicle, and the greater stability of cirrhotic tissue changes in this region in contradistinction to the labile nature of infraclavicular infiltra-

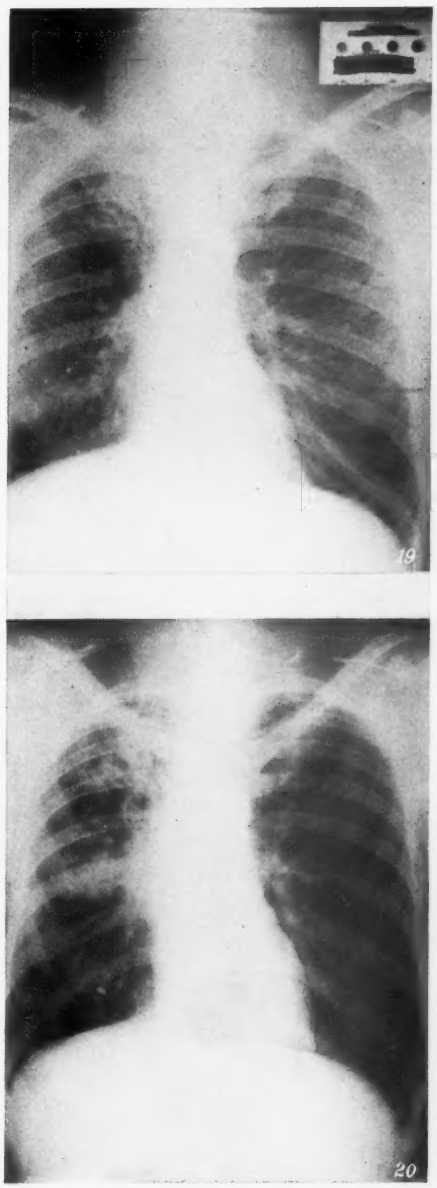
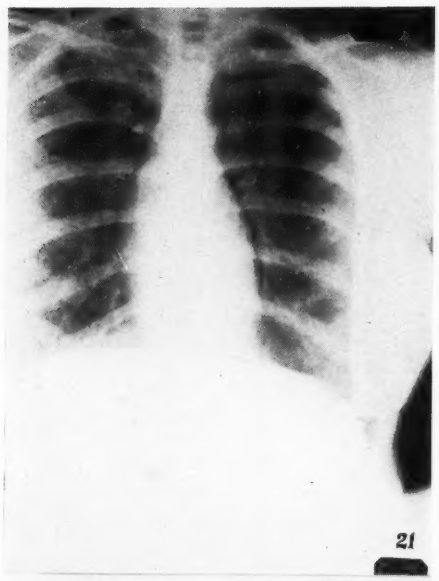


FIG. 19. August 12, 1929
FIG. 20. August 17, 1928



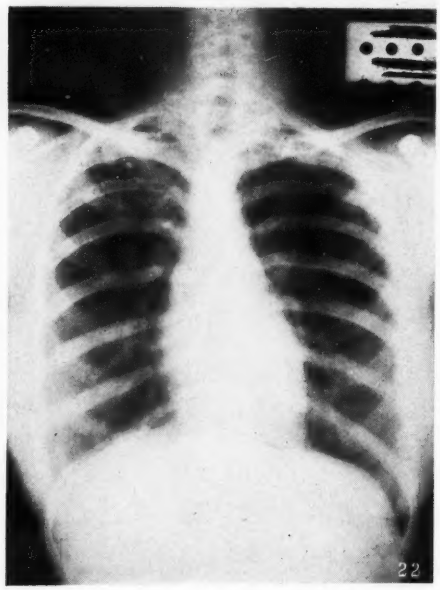


FIG. 21. December 12, 1926
FIG. 22. June 30, 1929

tive processes, have undoubtedly contributed to the overestimation of the significance of apical tuberculosis. Redeker distinguishes seven forms of apical tuberculosis, the majority of which are decidedly benign and cannot be considered as causative factors of progressive pulmonary tuberculosis. The solitary apical tubercle and the group tubercles described by Simon are, for instance, two benign forms. They are probably haematogenous metastases, which have occurred during childhood and may persist for many years without apparent changes in their X-ray appearance or without causing symptoms. Figures 21 and 22 give an example of group tubercles in a young girl who has been under our observation for the past four years. The round hard shadows in the apical field have not changed since 1926 and from clinical observation we have good reason to consider them as obsolete foci.

COMMENT

The fundamental difference between the newer views and the classical teachings must be clarified. There is, on the one side, the conception of an essentially acute infectious disease, which begins in any part of the lungs, with, and advances by, recurrent bronchopneumonic inflammations which are distinguished by a tendency to rapid retrogression or progression; and, on the other hand, the traditional views of an insidious onset, the development from miliary tubercles in the apical region, and the slow apicocaudal progression. The evidence in support of the recent teachings is so convincing that the old theory of an apical origin is undoubtedly on trial and its outcome is bound to cause radical changes in our preventive and therapeutic methods. The issue is of the greatest practical importance, and cannot be avoided by hair-splitting discussions of minor problems which are still a matter of debate. No one who is engaged in practical tuberculosis work can ignore Redeker's work, because our diagnosis, treatment and prevention of pulmonary tuberculosis are based on the old conception. Our physical exploration was focused on the apices. The chronic course of the disease created likewise the necessity of prolonged institutional care and conservative treatment, while in the field of prevention the existence of symptomless forms of beginning phthisis were never thought of. It is obvious, therefore, that our therapeutic and preventive methods will stand or fall with the foundations on which they rest. The discovery of the early infiltrate has revealed to us the limitations of our ability to diagnose the initial stage of the disease, which begins very often in a region where it cannot be

recognized by physical examination. The correct diagnosis is in many cases established too late, that is, at a time when tuberculosis has already spread to parts of the lung which can be explored by auscultation and percussion. Our treatment very often begins after the patient has already gone through the most critical period of his disease. Since success or failure of treatment, and of all preventive measures, depends primarily on our ability to recognize the onset of pulmonary tuberculosis, and to treat and to separate potential sources of infection, it follows that we will have to use serial and regular radiographic examinations as a routine method in the office and dispensary, particularly in all contact cases.

The acute development from infiltrations may also explain the rather puzzling fact to which Douglas, Pinner and Wolepor have called our attention, that the number of incipient cases that come under our observation is too small to account for the high percentage of far-advanced lesions that are reported from public and private sanatoria. The incipient stage of pulmonary tuberculosis is either not recognized in time, or the majority of patients reach the far-advanced stage in a much shorter time than we could expect with a slow apicocaudal extension. The alarming incidence of far-advanced forms is hardly explained by the delay in the diagnosis, and so the question arises of whether the new conception of pulmonary tuberculosis does not call for a revision of our therapeutic principles.

From the mere fact that in the course of the disease acute exacerbations occur which resemble surgical conditions, inasmuch as they demand immediate attention and very often prompt action, the necessity of provisions for immediate admission to our public institutions is justifiable. The fight against tuberculosis in Germany is already based on the discovery of the early infiltrate, and patients with such lesions can be referred, and are admitted, to a sanatorium without any delay. The allergic infiltrative focus is so labile that time is an important factor. As the development, either to resolution or to progression, takes place in a very short time, pneumothorax in time may decide between a localized infection or a rapidly advancing tuberculosis. During the allergic phase all stimulating therapy should be refrained from, while general and functional rest is strictly indicated. Since we had the occasion to observe cases of early infiltrations, we have made use of surgical collapse at an early date, whenever the tendency to progression was noticed, and although the time is too short to give, at present, a conclusive report, we should like to say that the results are so far very encouraging.

Another consideration, equally important, concerns beginning cavitation. Our therapeutic results with conservative methods are on the whole good but far from satisfactory, especially in the patients without means, for sooner or later these patients will break down. Compared with other respiratory infections, tuberculous infections are, after all, mild, and a true death from tuberculous infection as such is rare. Most of the patients die from secondary pathological changes in other organs, or from complications arising from their cavities, which are a source of flowing reinfection. The question must be raised as to whether our results would not be improved by the early obliteration of cavities.

It is hard to explain why the tuberculous focal infection caused by a hole in the lungs, which is filled with purulent and infectious material, has not led to a more active therapy, while teeth, tonsils and other organs, that may harbor foci of infection, are readily removed. It seems that one of the problems in the treatment of pulmonary tuberculosis is the prevention and early obliteration of cavities. We know that it is very difficult to close up a late encapsulated cavity with surgical measures, whereas the compression and obliteration of the early cavity is comparatively easy. We are led to believe that in the treatment of early infiltrates, which do not undergo spontaneous retrogression, or which show a tendency to progression and cavitation, surgical measures should be applied at an early date.

The detection of the early infiltrate, with its unobtrusive symptoms, will offer a real problem to public-health authorities. Before the disease manifests itself the infection can be spread in schools, households, boarding-houses and workshops, and it will be the task of dispensary workers to go more systematically than heretofore after the incipient case, and to provide for speedy hospitalization. It will be the duty of the dispensary, not only to find the incipient lesion by systematic and regular X-ray examination, but also to establish the mode and the source of infection.

CONCLUSION

1. The newer views, of which Redeker is the foremost exponent, are supported by statistical data and clinical observation.

2. Pulmonary tuberculosis begins often with nonapical infiltrations, which may undergo retrogressive changes, or may progress, causing extensive involvement of the lung in a short time.

3. Apical tuberculosis is, as a rule, a benign late form; the evolution of progressive disease from apical lesions is a comparatively rare occurrence.

4. Roentgen examination is the only method by which we can exclude pulmonary tuberculosis, which begins with nonapical infiltrates. Radiography of the chest should be used as a routine method.

5. Surgical collapse should be attempted in the treatment of infiltrations that do not retrogress spontaneously.

6. During the allergic phase general and functional rest are strongly indicated, whereas the use of any stimulating therapy, such as tuberculin, exercise, heliotherapy, etc., must be opposed.

7. Every effort should be made to diagnose acute infiltrations, and to hospitalize patients with this type of lesion immediately.

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THE CALCIFICATION OF TUBERCLES BY MEANS OF IRRADIATED ERGOSTEROL IN EXPERIMENTAL CHRONIC TUBERCULOSIS[1]

TOM DOUGLAS SPIES[1]

In a previous publication (1) it was demonstrated that calcification of the lesions of acute tuberculosis could be produced by means of large toxic doses of irradiated ergosterol. It then seemed of interest to study the effect of this substance on the lesions of animals with chronic tuberculosis. It is well known that spontaneous calcification occurs at times in chronic tuberculous lesions. In the experiments to be reported the degree of calcification occurring in the lesions of animals treated with irradiated ergosterol has been compared with that in a series of controls.

MATERIAL AND METHODS

Ten young rabbits, averaging 2380 gm. in weight, were given, each, intravenously, 1 cc. of a heavy saline suspension of avirulent bovine tubercle bacilli. Later a concentrated preparation of activated ergosterol,[2] having one thousand times the antirachitic potency of codliver oil, was administered by stomach-tube to four of the above rabbits in individual doses of 5 to 10 cc. This medication was begun on the 172nd day of the experiment, and was continued at frequent intervals (two to five days) until death occurred.

Three of the remaining 6 rabbits were given comparable doses of the inert solvent oil used in the above preparation. The other 3 rabbits received no medication and served as additional controls. All animals that were treated with irradiated ergosterol were allowed to die, and all the control animals were killed at about the same time as the test animals.

The tissues from all animals were fixed in an alcohol-formalin mixture (9 parts of 95 per cent alcohol to 1 part of 40 per cent formalin) in 10 per cent formalin, in 95 per cent alcohol, and in Zenker's fluid. Some of the tissues fixed in formalin were embedded in celloidin, and later stained either with haematoxylin and eosin or by the silver method of von Kossa. In order to demonstrate fat, frozen sections of formalin-fixed material

[1] From the Pathological Laboratory of the Boston City Hospital, Boston, Massachusetts.

[2] This preparation was furnished through the courtesy of Mead Johnson & Company.

were stained with Sudan-IV. The tissues fixed in Zenker's fluid were embedded in paraffin and stained with eosin-methylene blue, and by the usual method for the demonstration of tubercle bacilli in sections. The calcium deposits were identified by their solubility in acid and by the following histological criteria, using formalin-fixed material: (1) when stained with haematoxylin and eosin the precipitated calcium appeared as a dark blue, coarsely granular material; (2) after treatment with a silver-nitrate solution and counterstaining with 0.5 per cent basic fuchsin the deposits assumed a deep brownish-black color.

OBSERVATIONS

All animals were fat and healthy-appearing until a few days after the administration of irradiated ergosterol was begun. As the administration of this substance continued they began to lose weight rapidly, and death occurred in from nineteen to thirty-eight days after the initial dose.

Whereas all organs were examined grossly and microscopically in every animal, only the tubercles in the lungs and kidneys were regarded as sufficiently calcified to warrant their description in this report. Occasionally calcified tubercles were found in the spleen. In no instance did the lesions of the liver show calcium deposits.

GROSS PATHOLOGICAL DESCRIPTION

The gross appearance of the lungs of all the animals with tuberculosis was the same, whether or not they had received medication. The kidneys, on the other hand, showed certain differences due to deposition of calcium.

Lungs: Widely separated, grayish-yellow elevated nodules (tubercles) were scattered over the pleural surfaces of the lungs of 9 of the 10 animals examined. (The tenth animal, one of the control series, showed no evidence of tuberculosis.) These nodules were sharply demarcated from the adjacent tissues, and ranged from 0.5 cm. down to 0.2 cm. in diameter. They often contained sharply limited central yellow opacities. In the parenchyma were a very few similar nodules. The bronchi and vessels were negative.

Kidneys: Sparsely scattered over the external surface of the kidneys of 6 of the 10 animals were elevated nodules (tubercles) similar in appearance to the pulmonary lesions described above. In the kidneys of 2 of the 4 animals that received irradiated ergosterol were small grayish-yellow deposits (calcium) in the cortex and medulla.

MICROSCOPIC DESCRIPTION

Formalin Fixation

Lungs: Calcium deposits of irregular size and shape were located in the degenerated central portions of the tubercles of all the animals that received irradiated ergosterol. In contrast to these lesions, calcium was not

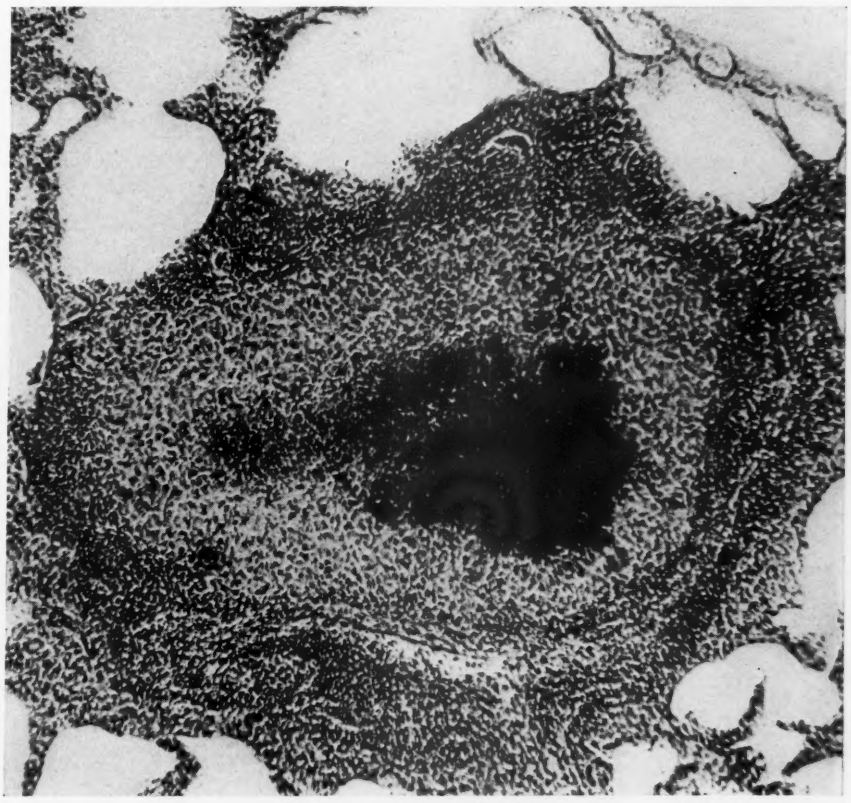

FIG. 1. Shows a well demarcated tubercle containing calcium deposits within the degenerated portion. × 15.

demonstrable in the non-necrotic tubercles. Enmeshed within the calcium deposits of the tubercles were necrotic cells, fat globules and an occasional acid-fast bacillus. Immediately surrounding the calcified areas of degeneration were many large mononuclear cells ("endothelial leucocytes", "epithelioid cells"). These were in turn surrounded by a

well-demarcated margin of connective tissue and lymphocytes. The large mononuclear cells and the margin of connective tissue and lymphocytes were free from deposits of calcium. In no instance was there any apparent change in the size, shape or cellular content of the tubercles following the deposition of calcium.

FIG. 2. Shows a partially organized thrombus within a large pulmonary artery. Note the heavy deposits of calcium within the thrombus. × 15.

Marked calcification of the bronchial cartilages and of the alveolar and bronchial walls occurred in 2 of the 4 animals that received irradiated ergosterol. In one of these a partially organized thrombus almost filled a large branch of a pulmonary artery. This thrombus contained heavy deposits of calcium.

Deposited calcium was absent from the tubercles of 2 of the 3 control

animals that received the inert solvent oil. Rare tubercles from the lungs of the third animal did contain minute deposits of calcium. The tubercles from one of the control animals which received no medication showed no deposited calcium. In those from the second animal were rare minute areas of calcification. The third animal in this series showed no evidence of tuberculosis.

It is thus clear that the spontaneous deposits of calcium that occurred in the pulmonary tubercles of 2 of the 5 controls having chronic tuberculosis were insignificant, compared with the large areas of calcification occurring in the tuberculous lesions of all animals that received irradiated ergosterol.

Kidneys: Three of the four animals that received activated ergosterol showed tubercles in the kidneys, as did 3 of the 6 control animals.

The renal tubercles of the animals treated with irradiated ergosterol contained deposits of calcium identical in appearance with those in the pulmonary lesions already described. Also many of the tubules, vessels and glomerular capsules were calcified, as described by Spies and Glover (2). Occasional tubercles in one of the 3 control animals having renal tuberculosis contained calcium deposits. These were smaller than the majority of the deposits in the tubercles of the animals that received irradiated ergosterol.

Zenker's Fixation

Calcification was absent from all tissues fixed in Zenker's fluid as the acetic acid had removed the precipitated calcium from the tissues. The pulmonary and renal tubercles from the animals that received irradiated ergosterol appeared identical with those from the control animals. Hyalinization of the arteries, veins, tubules and glomerular capsules was present (2).

DISCUSSION

It has been shown previously (1) that marked calcification of the necrotic and caseous centres of the tubercles of the lungs could be produced by the use of large doses of activated ergosterol in the late stages of acute tuberculosis in rabbits. It has been demonstrated in the present report that massive doses of activated ergosterol caused precipitation of calcium in the tubercles of chronic tuberculosis in rabbits, of a frequency and degree that was far greater than the slight spontaneous calcification of the controls. In both the acute and the chronic tubercles the calcium

deposits were almost entirely limited to the necrotic and caseous portions of the tubercles.

The dangers of applying these findings to patients with tuberculosis are obvious when the toxic manifestations of massive doses of irradiated ergosterol are considered. Degenerative lesions are found in the aorta, kidneys and other organs. It may be, however, that activated ergosterol can be given in such doses as to mobilize calcium and cause its deposition within tuberculous lesions without damage to the vital organs. Further experiments are needed to determine this point.

SUMMARY

It has been shown that the repeated administration of large doses of activated ergosterol to rabbits with chronic tuberculosis produces, as in acute tuberculosis, calcification within the necrotic and caseous portions of the tubercles.

I am indebted to Dr. F. B. Mallory for helpful criticism and for the photomicrographs.

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THE RELATION BETWEEN ALLERGY AND IMMUNITY IN TUBERCULOSIS[1]

MAX PINNER

Teleology . . . . has never been lucky in medicine.—*Rudolf Virchow, 1849.*

The relation between allergy and immunity is the subject of many experimental and clinical studies, whose basic question was and is: Do allergy and immunity go parallel or not? Much ingenious experimentation and much labored thought have been spent in an effort to elucidate the nature of the apparently unbreakable link between the two phenomena. The final result of all these studies leaves one in a singularly unsatisfied state of mind. Parallelism and interdependence can be—and are—shown just far enough to make apparent breaks seem particularly annoying to the mind which strives for law and order. In view of the facile manner in which the term "immunity" is used, one might expect that it has a definite meaning, be it by well agreed-upon definition, by etymology, or by description. Even the most cursory review of immunological literature reveals a disconcerting variety of meanings.

The following phenomena are considered as proof of existing immunity: (1) absence of demonstrable reaction; (2) increased reaction (as compared with nonimmune controls) locally or generally; (3) decreased reaction; (4) acute death; (5) final survival after (1), (2) or (3) may have occurred; (6) the presence in the blood of so called antibodies, such as antitoxins, agglutinins, opsonins, etc. It is possible to make a case by more or less elaborate circumlocution for each one of those criteria. Two points can obviously be concluded: (1) that the processes ensuring immunity are different in different diseases, and (2) that, instead of a generally accepted definition of immunity, there exists at the present time a multiplicity of uses, and a general vague notion that any given reader will approximately understand what any given writer means by the term.

This terminological chaos is maintained by what may be called the *pars pro toto* tendency in immunology, that is, the (usually all too) silent assumption that immunity exists because a phenomenon customarily

[1] From the Wm. H. Maybury Sanatorium (Detroit Municipal Tuberculosis Sanatorium), Northville, Michigan.

associated with immunity makes its appearance. *Example*: Immunity exists because agglutinins are present. No doubt exists as to the existence of different mechanisms of immunity in different diseases, but it is less realized, and not sufficiently emphasized, that different organs may have different methods of attack. In a discussion of tuberculosis, it is pertinent to realize that in the pulmonary parenchyma the defensive potency has not been detailed to specified structural elements, as in skin or bronchi for example. Functionally, the main defensive reactions of the lung are exudation and fibrosis, that is, processes which temporarily or definitely impair the vital function of the lung, while organs more specifically equipped for defense are not necessarily crippled while an offensive agent is removed. Is this not one of the reasons why in regard to some pulmonary conditions it is entirely a matter of faith (and not of fact) to call them either "adequate responses" or "diseases?" Pneumonia and pneumonoconiosis are illustrative examples. In the face of all these complicating matters, it is deemed safest to adopt an unequivocal and broad definition: Immunity is a condition which is, in a specific way, subservient to the existence of the biological entity whose integrity is attacked by a specific agent. Such a definition is undoubtedly too inclusive, but if in every instance due consideration is given to constitutional and environmental factors, it allows—at least—to measure immunity (always as compared to nonimmune individuals) in terms of survival or the amount of damage done. Throughout the present discussion, "immunity" is used in this sense only.

It is quite true that the same type of processes is apparently responsible for immunity in some allergic animals and for hastened death in others. Since the allergic reactions with their coincidental and consequential phenomena are known to be so intimately connected with protection, they have been called generally, and unjustifiedly, "immunity reactions," regardless of their ultimate results. Reports of animals who succumb quickly *because* they are "immune," frequent not only in the literature on tuberculosis, admit *per se* a divorce between the science of immunology and reality. That so called "immune" animals (*sc. l.*, animals which have been immunized) are, under certain conditions, more liable to rapid death is frequently explained as "immunity gone wrong;" in more scientific parlance, the term of preference is "the paradoxical nature of immunity."

There can be no doubt about the reality and validity of the observations that allergic animals are either more resistant to an infection than normal

animals or less so, but it should be clearly stated that it is the *state of allergy* which carries this double-faced potentiality, and not the state of immunity; the identification of allergy and immunity is based on only half the available evidence. The fundamental importance of the problem for therapeutic and prophylactic work cannot be doubted. It would be desirable to have the following questions answered: Is allergy desirable or not, is it instrumental in warding off reinfection, does it mitigate the destructive results of reinfection, does it promote healing processes? For allergy can be produced at will in the normal organism, it can be enhanced, and it can probably be depressed in the allergic organism; and—last, not least—its presence can be demonstrated, and—to a certain degree of accuracy—its intensity can be measured.

One may catalogue the evidence in favor of a parallelism of allergy and immunity:

Experimentally, it is shown convincingly that in tuberculosis both phenomena are produced by and are dependent on the same condition, and it has never been possible to immunize a susceptible animal without rendering it allergic. Certain phases in the allergic reaction (such as the "fixation" of bacilli) are evidently instrumental in tuberculoimmunity. Clinically, the great frequency of healing and completely healed foci or reinfection should be pointed out. Fibrosis seems to occur only in allergic soil. And here follows the evidence against the alleged parallelism, to wit: Only an allergic animal can be killed within a brief time by an infection with tubercle bacilli. Only in allergic soil does an infection ever cause acute and toxic conditions with their concomitant grave clinical picture; only in allergic soil does an infection ever cause acute exudative foci with rapid caseation and tissue destruction. Koch's phenomenon in the skin of an experimental animal is a quickly healing ulcer which apparently protects the animal from bacillary propagation; the same event in a human lung opens the scene for bronchogenic spread, —the most frequent single cause of death in pulmonary tuberculosis.

In considering the healing processes, lack of definite observational data complicates matters. Healing in a nonallergic organism cannot be observed, because the focus to be healed must have produced allergy already. There remains the question of whether a higher or lower degree of allergy is the more favorable condition for healing. It seems that rapid resorption of exudate occurs only under the same conditions under which it develops, namely, high allergy. Whether competent fibrosis develops more readily under conditions of a low degree or high degree of allergy

is open to discussion. Most important of all is the frequent observation of a simultaneous healing and progression in the lung of the same patient, which makes it at once evident that both healing and progression may proceed under the *same* conditions of allergy. Scanning over the clinical evidence, a decided lack of parallelism between allergy and healing processes is apparent; and, if healing be a manifestation of immunity, a lack of parallelism between allergy and immunity must be registered. The lack of this theoretically expected parallelism has produced such clinical inconsistencies as "healing by excavation" or "miliary tuberculosis, an immunization in grandiose style;" or it has been said that tuberculosis in primitive races is a disease in nonallergic soil, although the first few weeks of the disease are more than sufficient to establish allergy, and although the lesions in such individuals,—as well as the clinical course,—bear all the earmarks of acute allergic reactions, but, immunity being apparently absent or low in these individuals, allergy is requested to be absent by the theoretical expectation. All this confusion is undoubtedly caused by the desire to carry through to a logical completion the incontestable parallelism of allergy and immunity, in their genesis and causation.

Briefly, the development of thought is as follows: Immunity never exists without allergy; they are both caused by the same mechanism, and *only* by this mechanism. In every allergic animal, a certain degree of immunity can be demonstrated by *appropriate methods*. Hence, an absolute parallelism is postulated. Where apparent exceptions to this rule are observed, something went "wrong" before immunity had a chance to achieve its aims. The existence of this immunity is insisted upon; its "good intentions" are asserted, regardless of the most devastating practical results. Terminological cloaks are invented, to maintain the postulated parallelism between allergy and immunity.

Obviously, there must be an error somewhere in this concept. An analysis of the meaning of the terms *allergy* and *immunity* appears to be helpful. Allergy means the altered reactivity of the organism following an infection. The term is an abstraction to indicate a known effect of a known cause. We are not concerned here with the various aspects of the allergic reaction; we are only concerned with the fact that allergy designates a condition which is defined by its causation. *Methodologically speaking, allergy is a causative term.*

How about immunity? This term is not defined by its causation, but by the ultimate aim it is expected to accomplish. *Methodologically*

speaking, the term immunity is not a causative, but a teleological term. It is not intended here to discuss the respective merits of causative and teleological thinking. Whether the causative nexus is more than an empirically established sequence of events seems still to remain an open question in philosophical discussion. And the heuristic value of teleology has been demonstrated so convincingly in biological work that this method of reasoning cannot be left in the limbo to which some thinkers wish to have it confined.[2] For the sake of clarity of terminology, it is necessary to be conscious of the method of one's thinking and to avoid the methodological error of using causative and teleological terms (and consequently concepts) in the same chain of thought.[3]

This discussion is not concerned with methodological niceties, but, when methodological errors endanger the rational interpretation of perfectly good and clean-cut observations, the obstacle should be recognized. And here is the obstacle: It is attempted to establish a *quantitative* relation between a phenomenon defined by its causation (allergy) and one defined by its purposive (teleological) significance (immunity). This is logically as impossible as to evaluate the muscular contractions of the stomach in moral terms, although the bearings of hunger on moral conduct are not denied. Immunity cannot be measured in terms of allergy, nor is the reverse possible, because allergy and immunity are noncomparable conditions,—one an abstraction of causative, the other an abstraction of teleological thinking. The question, "Does immunity go parallel with allergy?" can logically not exist.

Allergy is a condition which is strictly defined by its cause. Its existence can be ascertained in any given case by applying such measures as are known to be appropriate to cause an allergic *reaction.* (It is a most noteworthy fact that nothing is known of the *condition* allergy, but only of some reactions caused by this condition.) Certain characteristics of the allergic reaction are well known; some of them may be interpreted as being useful to the maintenance of life (for example, the prevention or diminution of bacillary spread from the site of reinoculation); others

[2] ". . . . the difficulty of avoiding 'teleological' modes of expression in biology rests partly upon the fact that in an organism the parts constituting it are so related to one another and to environmental events that typically the organism endures" (J. H. Woodger, *Biological Principles*, Harcourt, Brace & Co., 1929, p. 440).

[3] "It seems probable that the antithesis between teleology and causation depends very largely upon three factors: (1) insufficient analysis of these notions themselves; (2) too great haste in trying to bring them into relation; (3) assuming them to be mutually exclusive" (*l. c.*, p. 450).

should be interpreted as being harmful to the biological entity (such as the systemic reaction or possibly the circumfocal hyperaemia around older foci). Can it be stated then that either the "beneficial" or the "harmful" processes are manifestations of the allergic state? In other words, can it be decided whether immunity or hypersusceptibility is by necessity linked with *allergy*? Here, it becomes evident that allergy does not lend itself to a teleological interpretation.

Immunity is defined in terms of a purpose, since immunological reactions are (by definition) purposeful processes. In any given instance, immunity depends not only on the condition of the organism in question, but on extrinsic factors as well (such as dosage and virulence of infecting microörganisms, portal of entry, etc.). It depends greatly on these extrinsic factors whether the final result of an allergic reaction is favorable or unfavorable for the biological entity; in other words, whether allergy had in its train immunity or hypersusceptibility. Since either possibility exists, it is impossible to decide which event is by necessity connected with the allergic state. Here is apparent the impossibility of establishing a causal nexus between allergy and immunity.[4]

Another methodological difference between allergy and immunity must be pointed out. In every allergic reaction, the same characteristics can be observed, regardless of its final result. What we call immunity is achieved by processes which vary in their essentials. In acquired immunity is seen the rapid and energetic tissue response (that is, the allergic reaction); in naturally immune animals, such as rats, immunity is achieved by an absence or paucity of tissue responses. Here, a hyperactive reaction; there, lack of reaction, either representing what we call immunity. The fact that fundamentally so divergent phenomena are called by the same name shows clearly how large the factor of interpretation must be in the concept "immunity."

It would appear that allergy and immunity are not two biological conditions, which may be either independent of each other, or which are closely linked together, or identical. A logical inquiry shows that allergy and immunity express two essentially different viewpoints of the observer.

[4] "Any change in an organism, following an environmental change, either subserves the persistence of the organism or it does not. If the former is the case, we can call it an 'appropriate' response. Now, with our present ways of thinking, there appear two ways of regarding such an occurrence. We can either ask: Did this happen 'appropriately' *in order that* the persistence of the organism should ensue? Or, we can ask: Did this just happen in this way, and it 'happened' to be appropriate?" (*l. c.*, p. 439).

The existence of either one can be ascertained only by submitting the organism in question to a reaction caused by the specific agent (or certain of its derivatives). In observing such a reaction, the causalist will ask: Has the reaction those criteria which are regularly present in previously infected (or sensitized) individuals?—and his answer will be that the individual is allergic or not. The teleologist, observing the same reaction will ask: Is the state of the individual of such a nature that its integrity is better, less, or equally well protected as—under the same circumstances—a similar individual which is known to be "normal"?—and his answer will be that the individual is immune, or hypersusceptible, or immunologically normal.

The difference in point of view (that is, interest) which is expressed in the terms *allergy* and *immunity* could be illustrated by many simple similes. In order to stress and clarify the point of contention, one such simile may be quoted. A given rainfall may be studied in regard to its causation (barometric pressures, temperatures, etc.) (the causalist who would choose to speak in terms of allergy); or it may be studied in regard to its desirability for the crops (the teleologist who would choose to speak in terms of immunity).

It appears from the foregoing that the term *immunity* could probably be dispensed with in a great many instances. That its use as corollary to allergy is incorrect has been shown; that it is in no way needed in this connection is evidenced by the truism that a *complete* description of the allergic reaction will *per se* include all those factors which—for the teleologically minded—signify immunity or its reverse. This promises more clarity, and more justice to the concept that immunity is an incidental consequence of the mechanism which causes allergy, and that it may or may not become apparent when put to the test. For all theoretical and experimental work, the restriction of the use of the term immunity to its actual meaning, regardless of the mechanism achieving the result, would undoubtedly clarify many obscure issues.

Does the term immunity serve a useful purpose in clinical work? Its abundant use would indicate so. However, it should be remembered that no procedure is known to demonstrate or measure immunity. The frequent saying that a patient has a good immunity means nothing more nor less than that he *has* done well up to the time of observation, without guaranty that he will continue to do so. It is, however, in no way permissible to ascribe all healing processes to specific immunity; constitutional factors, environmental influences, mechanical conditions in the

local lesion: they and many more factors decide the clinical course. The limited part which immunity *sensu strictiori* plays in the course of the disease should be clearly recognized in order to do justice to such therapeutic measures which are likely to aid in the nonimmunological problems. If then, clinically, immunity is only a somewhat rough translation of a simpler clinical term, it may as well be omitted, particularly since its use seems to include an unwarranted promise for the future.

What then is the outcome of this lengthy discussion? The attempt to correlate allergy and immunity quantitatively is doomed to failure, because the two terms are incomparable concepts. Immunity cannot be measured in terms of allergy for the identical reason. The clinician should not try to correlate a strong tuberculin reaction with high immunity, nor will he find the reverse relation to hold true. The elusive nature of immunity, whose doings are obscured by many extrinsic factors, cannot be recognized nor measured until the disease has run its course.

The elimination of the term *immunity* from clinical usage will more clearly show the pressing need to study carefully the influence which allergy has on pathological processes. It should be possible by close clinical observation to decide definitely whether a high or a low degree of allergy influences, favorably, resorption, fibrosis, calcification. The fact that the answers to such questions are not available to-day deprives us of the opportunity to use one possibly powerful weapon against the disease, namely, the controlled alteration of the intensity of the allergic state.

SOME RESULTS OF TUBERCULOSIS ADMINISTRATION IN CATTARAUGUS COUNTY, NEW YORK[1]

JEAN DOWNES AND EDGAR SYDENSTRICKER

As a part of an experiment in rural health administration, the Milbank Memorial Fund aided the Cattaraugus (New York) County Board of Health in putting into operation certain antituberculosis activities which have been continued since 1923. In this paper an attempt is made, from the available records, to judge the degree of success of these activities in various terms, such as case-finding, supervision of active cases, and death-rates. For it is obvious that antituberculosis work is not an effort directed toward a single objective; its objectives are several, each involving a different kind of activity and calling for specific modes of measuring results. It includes efforts to prevent minimal tuberculosis; to prevent the development of minimal cases into more serious stages; to arrest more advanced cases; and to arouse the community to its responsibility in keeping the arrested cases well. No single measure is adequate for evaluating precisely the complete results of so varied a program.

It should be emphasized, as has been intimated above and as will be perfectly evident, that the records used in the analyses which follow were not especially designed for the purpose of measuring the results of antituberculosis activities, but were primarily for administrative use. Furthermore, some changes in diagnostic classification occurred, information important from the point of view of evaluation was frequently lacking, and the entries on the record at times did not lend themselves to numerical expression. Hence this study of necessity is confined to those data which lent themselves to statistical treatment. No qualitative appraisal of the Cattaraugus experience is attempted in this paper except in so far as the statistical record may afford grounds for qualitative interpretation.

[1] From the Division of Research, Milbank Memorial Fund. Acknowledgments are made to Dr. John H. Korns, Director of Bureau of Tuberculosis, Dr. R. M. Atwater, County Health Officer, and Miss Frances King, Statistician, Cattaraugus Department of Health, for making available the data used in this study and other assistance; to Dr. G. F. Warren, of the State College of Agriculture, Cornell University, for the economic data used in this study; and to Mr. Homer Folks, Mr. George J. Nelbach, Dr. James Alexander Miller and Dr. Linsly R. Williams, as well as Dr. Korns and Dr. Atwater, for reading the paper in manuscript form.

Cattaraugus County, having a population of approximately 72,000,[2] with 31,000 living in the two urban communities, Olean and Salamanca, and 41,000 dwelling on farms or in small villages, has had a relatively low death-rate from tuberculosis over a long period of time. In 1880 and 1890 the death rates from "consumption" were 132 and 108 per 100,000 population respectively.[3] The accompanying figure (1) indicates that the death-rate from 1900 to 1923 has shown only a slight decline with annual variations above and below a trend line.[4] The experience of Cattaraugus in this respect is not unlike that of one or two other rural counties in New York State. Why Cattaraugus County has had such a favorable rate we are unable to say. But feeling assured that the mortality record is reasonably accurate, it may be stated that the intensive antituberculosis work in Cattaraugus was undertaken in an area where the death-rate from the disease was already relatively low and had been on a low level for some years. A further reduction of the death-rate under such conditions thus becomes an experiment of unusual interest.

1. ANTITUBERCULOSIS WORK IN CATTARAUGUS COUNTY PRIOR TO 1923

The status of antituberculosis work in Cattaraugus County previous to 1923, when the Bureau of Tuberculosis was organized, may be reviewed briefly before referring to the later activities and the indications of their results.

Antituberculosis work was started in 1909 by the organization of the Cattaraugus County Tuberculosis and Public Health Association. The Olean society maintained a tuberculosis nurse for the city of Olean, established an open-air school and initiated a children's health camp. As a result of the public educational work of the County Association and several of its branches, it was decided in 1913 to establish a county sanatorium at Rocky Crest. The county sanatorium was opened in 1916 and during the period 1916–1923 had a bed capacity of 32, which was 18 beds less than the minimum standard based on a bed for each annual death. As in most New York counties, the county sanatorium was established primarily as a place to segregate patients with advanced tuberculous disease in the hope of reducing the spread of infection. Con-

[2] Excluding Indian population, estimated as 1,000. Census enumeration showed the Indian population 1,162 in 1920 (*XX Census Volume III, 678*) and 927 in 1925 (*State Census Enumeration, 1925*).

[3] Data obtained from *U. S. Census 1880, Vol. XII and U. S. Census 1890, Part IV*.

[4] The trend line here used is a straight line fitted to the rates for 1905–1923. The slope of this line (value of b) was -1.0202 ± 0.199 per 100,000 per year.

sequently, the principle that much of the effectiveness of the sanatorium depends upon its ability to serve the minimal case was not stressed and there was no provision for children.

The County Association employed a tuberculosis nurse whose headquarters were at the sanatorium, and the greater part of her time was utilized in home bedside nursing, transporting patients to and from the sanatorium, follow-up of discharged patients, and assisting at the clinics. Tuberculosis clinics were held once a week in Olean and at irregular intervals at several points in the county. The clinic facilities were regarded as not of the best, especially in the more rural districts. The superintendent of the county sanatorium served as a clinician and was aided by the county nurse and volunteer workers. The annual report of the county nurse for 1920 and 1921 showed an average of 52 clinics held, with a total attendance of 235. Very few of those attending clinics were referred by private physicians.

2. ORGANIZATION OF COUNTY BUREAU OF TUBERCULOSIS IN 1923

The County Department of Health was organized in January, 1923, and the Bureau of Tuberculosis was established November 15 of the same year, under the direction of Dr. S. A. Douglass (1); in 1924 an assistant director, Dr. William C. Jensen, who was superintendent of the county sanatorium, was added to the staff of the Bureau. Upon Dr. Douglass's appointment as County Health Officer, Dr. Jensen was appointed Director of the Bureau of Tuberculosis, February 1, 1925, and was succeeded in January, 1928, by Dr. J. H. Korns, the present Director of the Tuberculosis work. During the period since 1923 clinics were established as follows: one in each of the six health districts; a weekly clinic at Olean, a city of some 23,000 population; a biweekly clinic at Salamanca, a city of 9,000 population; and a monthly clinic at Randolph, Cattaraugus, Ellicottville and Franklinville, four incorporated villages in the rural part of the county. The clinic schedule has varied during the years 1923–1929 according to the needs of the various localities. Table 1 shows the volume of clinic work and nursing service during this period. The tuberculosis clinics of the county Health Department were, in theory, and largely in fact, diagnostic clinics, referring positive cases to physicians for treatment. However, the Bureau of Tuberculosis has functioned so that the practising physician has had at his command at any and all times not only the services of a specialist in tuberculosis for

the purpose of consultation and advice, but also the assistance of public-health nurses in home supervision.

A generalized nursing service was in process of being developed during 1923–1924 and was finally organized in January, 1925, with a staff of twelve public-health nurses. These nurses were located at the several stations and substations in the rural part of the county. The nurses assist in case-finding, get in touch with known contacts and serve at clinics. Since the benefit received from a few weeks or months of sanatorium care may be nullified by unfavorable environment in the home, the nurses' most important service in the treatment of tuberculosis is the care and advising of home patients, the arrangement of their environment, and the continued or periodic contacts with patients.

TABLE 1

*Tuberculosis clinic service and nurses' visits as reported by the Cattaraugus County Health Department, 1923–1929**

	1923	1924	1925	1926	1927	1928	1929
Clinics held	19	144	174	142	123	113	114
Examinations	511	2,988	3,102	1,819	1,311	1,076	1,394
First examinations	484	2,434	2,446	1,082	725	553	804
Reëxaminations	27	554	656	737	586	523	590
X-rays	193	956	608	463	541	623	1,099
Nurses' visits, positive cases (excl. Olean City)	1,003	1,360	1,592	2,337	2,000	1,568	1,489

*From the Annual Report of Cattaraugus County Department of Health, 1929.

By 1926 the county sanatorium was well staffed, the bed capacity was increased to 50, and a new section was added for the care of children. The physical plant has been steadily improved, resulting in more comfort and a better morale among the patients.

The discovery of cases, which is essential in a tuberculosis program, has been accomplished in Cattaraugus County through seeking the co-operation of the private physician, through the work of the nurses, and through the medical examination of school children. In addition to these specific measures for the discovery of tuberculosis, there has been a general campaign of health education throughout the county. The purposes of this campaign have been to acquaint the community with the early signs of tuberculosis, and the necessity of prompt diagnosis and treatment, as well as to arouse interest in general community health.

3. THE DISCOVERY OF CASES[5]

Records of the annual number of cases, classifiable according to age, form, stage and activity, if comparable from year to year, are pertinent data upon which to base some judgment of the success of case-finding activities. Unfortunately this essential comparability of record in the Cattaraugus experience is lacking, with the possible exception of active cases in recent years.

The annual gross totals of cases reported as discovered in the period 1914–1929 are plotted as a solid line in figure 2. It will be noted that prior to the establishment of the County Tuberculosis Bureau in 1923 the reported cases were only slightly in excess of the deaths each year; that in 1923 and 1924 there was a marked increase in the cases as reported (311 in 1924); and that since 1924 the number of new cases reported has declined to a level of approximately 115 annually. The large number of cases reported in 1924 and 1925 reflects the results of a round-up of cases which presumably were active at the time or had a history of the disease. The great majority of these were not diagnosed as active; on the contrary, they were chiefly cases whose activity was not recorded, as table 2 shows:

TABLE 2

Number of tuberculosis cases (all forms) reported each year in Cattaraugus County, 1923–1929, and the extent of their classification as to activity upon diagnosis

YEAR	TOTAL CASES REPORTED	CASES RECORDED AS		ACTIVITY UNKNOWN EXCEPT BY DEATH*	ACTIVITY NOT RECORDED
		Active or quiescent	Arrested or apparently cured		
1923	124	32	17	22	53
1924	311	72	58	33	148
1925	197	59	59	12	67
1926	145	67	34	10	34
1927	108	68	18	6	16
1928	112	63	23	8	18
1929	119	55	44	10	10

* Including not only cases unknown before the death certificate was filed but also cases for which no information as to activity was available except the fact of death from tuberculosis.

With such a large proportion (48 per cent in 1924) not diagnosed from the point of view of activity, any comparison of the annual distribution

[5] All of the data for both cases and deaths presented in this study are exclusive of Indians and nonresidents at the J. N. Adam Memorial Hospital, Perrysburg.

of the new cases according to activity obviously would be open to question.

In fact, quite aside from such lacunae in the records as we have referred to, the possibility ought to be considered that, in the course of intensive case-hunting campaigns, there may be a tendency to make diagnoses of tuberculosis without sufficient evidence of anatomical or clinical disease. This possibility had been discussed at various times with reference to the Cattaraugus experience, and later in 1930 a partial review of the cases on the roster[6] indicated that the diagnosis of tuberculosis

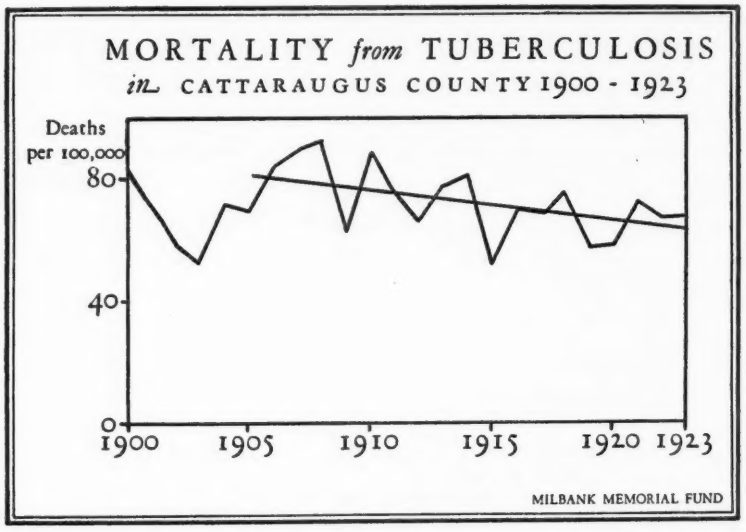

FIG. 1

had been too liberal, especially in the earlier years of the demonstration. A review of approximately half of 619 cases on the roster indicated that errors in diagnosis might average 5 per cent annually for cases originally classified as active, but 50 per cent for cases originally classified as arrested. Whatever may be the result of a review of the remainder of the roster, chiefly cases on which the evidence is incomplete, or of

[6] When Professor C.-E. A. Winslow undertook a general review of the public-health developments in Cattaraugus County the question was again raised by Dr. Herbert R. Edwards who was associated with Professor Winslow on the tuberculosis phases of the review. As a result, Dr. Edwards and Dr. Korns undertook a review of the entire roster of cases, with such evidence as the records, clinical and others, afforded.

further reviews of the roster, it is perfectly evident that any attempt to compare the distributions of the total cases according to activity, stage, form, source of first information, for successive years or periods is out of the question at present. Even if we should consider only those cases for which the diagnosis is regarded as accurate by those competent to judge, the weight accruing to certain types of cases by reason of greater possibility of accuracy would distort the distributions.

If the percentages of "error," referred to above, may be applied to the entire roster of cases, it may be possible to estimate roughly the annual number of cases which should have been classified as tuberculosis. This we have ventured to do, and the resulting estimates are represented by the broken line in figure 2.

The principal conclusion, however, to be drawn from the Cattaraugus experience in this report, is that it clearly points to the necessity, if any attempt is made to appraise accurately the results of case-finding activities, for maintaining *comparable* tuberculosis case records over the entire period to be considered. This postulate, simple as it is in principle, appears to be disregarded generally by those who are conducting antituberculosis work.

Ratio of Active Cases to Deaths: Obviously this is an extremely crude measure because so many factors, some of which have been suggested in the foregoing pages, are involved. In view of the fact that such a ratio is in more or less common use and is employed as a means of evaluating antituberculosis work in the American Public Health Association's *Appraisal Form*, it is given here for what it is worth. As shown in table 3, which is based on the original roster, the ratio for Cattaraugus County has increased from 1 in 1923 to 7 in 1927, declining somewhat in 1929.

4. RESULTS OF SUPERVISION OF ACTIVE CASES

The comments on active cases in the following paragraphs are based on the records of active cases after eliminating those cases whose diagnosis was "reversed" by Doctors Korns and Edwards in their review of the roster already referred to. As has been pointed out, the proportion of cases, originally classified as active, whose diagnosis was later "reversed" was relatively small.

Changes in the Activity of Cases from Year to Year: Some of the results of supervision of active cases are indicated in table 4. The active cases of tuberculosis (all forms) under supervision, classified as active at or as near as possible to the beginning of each year, have been tabulated

according to the change occurring during the year, that is, as to whether the case became quiescent, arrested, or died, or underwent no change in

TABLE 3

Ratio of active cases of tuberculosis (all forms) to deaths from tuberculosis

YEAR*	ACTIVE CASES*	NUMBER OF DEATHS	RATIO OF ACTIVE CASES TO DEATHS
1923	56	49	1.1
1924	115	46	2.5
1925	157	33	4.8
1926	202	32	6.3
1927	220	31	7.1
1928	202	29	7.0
1929	169	35	4.8

* Cases counted as of December 31, in each year.

TABLE 4

*Change in the condition of all known active cases of tuberculosis as of January first each year in Cattaraugus County, 1922–1929**

YEAR	TOTAL ACTIVE CASES	NO CHANGE	QUIESCENT	ARRESTED OR APPARENTLY ARRESTED	DIED		IN ADDITION THE NUMBER MOVED AWAY
					Tuberculosis	Other causes	
				Number			
1922	22	9	0	0	13	0	0
1923	43	18	0	2	22	1	2
1924	73	37	5	7	24	0	3
1925	106	56	6	28	16	0	12
1926	151	65	29	31	23	3	8
1927	168	62	34	51	19	2	12
1928	138	46	18	46	24	4	17
1929	125	46	25	35	18	1	12
				Per cent			
1922	100.0	40.9	0	0	59.1	0	
1923	100.1	41.9	0	4.7	51.2	2.3	
1924	100.0	50.7	6.8	9.6	32.9	0	
1925	100.0	52.8	5.7	26.4	15.1	0	
1926	99.9	43.0	19.2	20.5	15.2	2.0	
1927	100.0	36.9	20.2	30.4	11.3	1.2	
1928	99.9	33.3	13.0	33.3	17.4	2.9	
1929	100.0	36.8	20.0	28.0	14.4	.8	

* Cases under observation four months or longer.

the opinion of the diagnostician. No case is included in this tabulation which was not under supervision at least four months during the year.

Obviously the larger the proportion becoming arrested and the smaller the proportion dying within the year, the more effective has been the treatment of these cases.[7] In 1922 and 1923 half of the known active cases died before December 31, while since 1925 the proportion dying

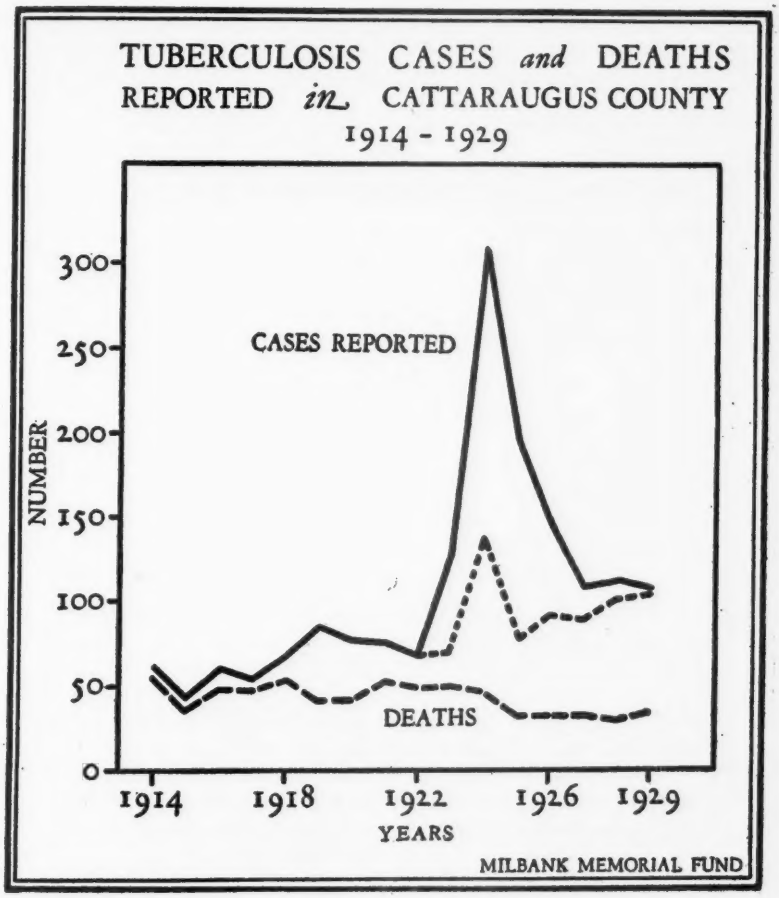

FIG. 2

within the year has averaged only 15 per cent. The proportion of cases in which activity has ceased within the year has increased from 5 per

[7] Provided, of course, that no radical change was made in the standards of diagnosis and classification. In this instance it does not appear that any such change occurred so far as active cases are concerned; any slight changes could not have affected the results materially.

cent in 1923 to an average of 30 per cent in 1927–1929. Since 1924 a third of the active cases in each year had some sanatorium care. In this connection it is of interest to point out that the sanatorium has improved greatly in respect to treatment of early tuberculosis. This is evident from a comparison of the cases treated in 1923, when the Bureau of Tuberculosis was organized, with those treated in 1929. Sixty persons having pulmonary tuberculosis were treated during the fiscal year ending

TABLE 5

*Change in the condition of all known active cases of adult pulmonary tuberculosis as of January first each year in Cattaraugus County, 1922–1929**

YEAR	TOTAL ACTIVE CASES	NO CHANGE	QUIESCENT	ARRESTED OR APPARENTLY ARRESTED	DIED		IN ADDITION THE NUMBER MOVED AWAY
					Tuberculosis	Other causes	
				Number			
1922	22	9	0	0	13	0	0
1923	42	18	0	2	21	1	2
1924	71	35	5	7	24	0	3
1925	97	51	6	25	15	0	12
1926	139	56	28	30	22	3	7
1927	144	52	31	40	19	2	11
1928	115	40	14	39	20	2	17
1929	94	34	25	19	15	1	11
				Per cent			
1922	100.0	40.9	0	0	59.1	0	
1923	100.1	42.9	0	4.8	50.0	2.4	
1924	100.0	49.3	7.0	9.9	33.8	0	
1925	100.1	52.6	6.2	25.8	15.5	0	
1926	100.0	40.3	20.1	21.6	15.8	2.2	
1927	100.0	36.1	21.5	27.8	13.2	1.4	
1928	100.0	34.8	12.2	33.9	17.4	1.7	
1929	100.1	36.2	26.6	20.2	16.0	1.1	

* Cases under observation four months or longer.

October 31, 1923. Of these, 15 per cent were classed as minimal, 33.3 per cent moderately advanced, and 51.7 advanced, as compared with 33 per cent minimal (including childhood type), 26 per cent moderately advanced, and 41 per cent advanced for the fiscal year 1929.

The foregoing record of changes in the condition of active cases may be summed up by saying that since 1924, 403 active cases (excluding those moving away) have been under supervision in Cattaraugus County.

Of these 31 per cent died of tuberculosis, 3 per cent died of other causes, 49 per cent became arrested during the period, and 18 per cent were active or quiescent at the end of the period.

If childhood type and nonpulmonary tuberculosis are excluded from the figures given above, the results for adult pulmonary cases, as shown in table 5, are not quite so pronounced. Three hundred and forty-two active cases of adult pulmonary have been under supervision in Cattaraugus County from 1924 to the end of 1929; of these, 34 per cent died of tuberculosis, 2 per cent died of other causes, 47 became arrested during the period while 17 per cent are active or quiescent. When we further classify these cases of adult pulmonary according to broad age-

TABLE 6

Change in the condition of all known active cases of adult pulmonary tuberculosis during the period 1924–1929 according to broad age-groups

AGE	TOTAL CASES	NO CHANGE	QUIESCENT	ARRESTED OR APPARENTLY CURED	DIED	
					Tuberculosis	Other causes
			Number			
0–19	39	6	1	18	14	0
20–39	188	19	13	94	60	2
40+	116	11	8	53	38	6
			Per cent			
0–19	100.1	15.4	2.6	46.2	35.9	0
20–39	100.0	10.1	6.9	50.0	31.9	1.1
40+	100.1	9.5	6.9	45.7	32.8	5.2

groups, as in table 6, very little variation in the results of supervision is shown for different ages. Approximately the same proportion in each age group died of tuberculosis, although those dying of other causes increase with age, as might be expected. The proportion (46 per cent) becoming arrested or apparently cured in the age-group 40 and over is the same as for ages 0–19 and is slightly less than for ages 20–39 (50 per cent). However, these differences can scarcely be considered significant.

Changes in the Proportion of Active Cases Which were Minimal, Moderately Advanced and Advanced: It is a well-known fact that the effectiveness of treatment and supervision of active tuberculosis cases is greatly influenced by the stage of the disease at the time the case is diagnosed. Table

7 shows the total active cases of adult pulmonary tuberculosis under supervision each year, classified according to stage. In 1922 and 1923 more than half of the active cases were classified as advanced, while in the last three years the proportion has been from 20 to 24 per cent. The proportion of minimal active cases has increased from 14 per cent in 1923 to an average of 27 per cent in 1927 to 1929. However, the proportion of moderately advanced cases has remained practically the

TABLE 7

Total active cases of adult pulmonary tuberculosis as of January first in each year classified according to stage, 1922–1929

YEAR	TOTAL CASES	STAGE			STAGE UNKNOWN
		I	II	III	
		Number of cases			
1922	20	1	5	14	2
1923	43	6	12	25	1
1924	73	8	37	28	3
1925	105	16	60	29	3
1926	138	28	80	30	8
1927	152	43	78	31	3
1928	133	37	66	30	0
1929	105	27	53	25	1
		Per cent			
1922	100.0	5.0	25.0	70.0	
1923	100.0	14.0	27.9	58.1	
1924	100.1	11.0	50.7	38.4	
1925	99.9	15.2	57.1	27.6	
1926	100.0	20.3	58.0	21.7	
1927	100.0	28.3	51.3	20.4	
1928	100.0	27.8	49.6	22.6	
1929	100.0	25.7	50.5	23.8	

same throughout the period, from 50 to 58 per cent of the active cases in each year being classified as stage II. This analysis brings out one of the difficulties encountered by those vitally interested in the preventive aspect of tuberculosis work. Quite often clinical symptoms of tuberculosis do not appear until the disease is moderately advanced and, unless cases can be discovered and given care before the disease is moderately advanced or advanced, the chances of treatment being effective are greatly lessened. The foregoing percentages indicate that this difficulty was to an appreciable extent overcome in Cattaraugus County.

The very great importance of "early diagnosis"—that is, the discovery of cases in the minimal stage—is further emphasized in the Cattaraugus experience when the progress of active cases is followed for a period of several years. The records enable us to do this for 52 active cases first reported or found in 1925, as shown in table 8. These cases were all active when reported; 27 per cent were classed as minimal, 54 per cent moderately advanced and 19 per cent were advanced. Fifty per cent of the cases had some sanatorium treatment during the period 1925–1929. The table shows the progress of these cases year by year to the

TABLE 8

History of 52 active cases of adult pulmonary tuberculosis diagnosed by or reported to the Cattaraugus County Health Department in 1925

DATE OF CLASSIFICATION OF CONDITION OF CASE	TOTAL	CONDITION OF CASE					NUMBER LEAVING COUNTY
		No change	Quiescent	Apparently arrested	Arrested or apparently cured	Died	
		Per cent					
By December 30, 1925	100.0	70.0	6.0	6.0	4.0	14.0	
By December 30, 1926	100.0	42.6	6.4	10.6	17.0	23.4	
By December 30, 1927	100.0	27.7	10.6	6.4	25.5	29.8	
By December 30, 1928	100.0	17.4	6.5	6.5	34.8	34.8	
By December 30, 1929	99.9	4.4	8.9	2.2	44.4	40.0	
		Number					
By December 30, 1925	52	35	3	3	2	7	2
By December 30, 1926	50	20	3	5	8	11	3
By December 30, 1927	47	13	5	3	12	14	0
By December 30, 1928	47	8	3	3	16	16	1
By December 30, 1929	46	2	4	1	20	18	1

end of 1929. In spite of the fact that a relatively small number of these cases were advanced when reported in 1925, 40 per cent of the total number had died by the end of 1929, only 13 per cent were still active or quiescent, while 44 per cent of the cases were arrested or apparently cured. A like tabulation of the 58 new active cases reported in 1926 showed strikingly similar results; 31 per cent of these cases were classed as minimal, 41 per cent moderately advanced and 28 were advanced. By the end of 1929, 43 per cent of the 58 cases were arrested, 16 per cent showed no change, 4 per cent were quiescent and 37 per cent had died.

Delay in Reporting of Cases an Unfavorable Factor: The foregoing paragraphs indicate at least some degree of favorable results of supervision upon the progress of the case as well as upon the mortality. It is only fair, however, to consider a factor which tends to oppose this result, especially from the point of view of mortality.

A prerequisite of an effective tuberculosis program is early reporting of cases. This is important in respect to both supervision of the case and the protection of those persons in contact with tuberculosis. Any serious deficiency in this function will be reflected in the tuberculosis mortality. Table 9 presents an analysis of the tuberculosis deaths during 1926–1929 according to the length of time the case was known before death occurred. From 6 to 11 deaths in each year were not known of *as cases* until after receipt of the death certificate, and from five to

TABLE 9

Tuberculosis deaths, showing extent of time between the reporting of the case and death, Cattaraugus County, 1926–1929

YEAR	TOTAL DEATHS	LENGTH OF TIME CASE WAS KNOWN				
		After death	Less than 6 months	6 months but less than one year	1 year to 3 years	3 years or longer
1926	32	11	8	1	8	4
1927	31	6	5	2	9	9
1928	29	8	8	2	7	4
1929	35	10	10	5	5	5

ten cases were known less than six months before death.[8] Reporting within six months of death affords very slight opportunity for effective supervision or preventive measures to be employed. That this presents a problem which is common to other areas is shown by Plunkett who states that "Of the total cases reported during 1926 (in New York State exclusive of New York City), 27.5 per cent either were reported after death or resulted in death during that year" (2).

5. CHANGES IN TUBERCULOSIS MORTALITY

The foregoing discussion of the records of case supervision pointed definitely to a reduction in the fatality of a considerable number of active cases. Obviously this ought to be reflected in the death-rate.

[8] It is fair to point out that from one to three deaths each year during 1926–1929 were of nonresidents with advanced active disease who were in the County less than four months.

Change in the Trend of Mortality: Considering now the recorded tuberculosis mortality statistics, such a result is indicated by a change in the period 1925–1929 from the previous trend. The significance of the decline in mortality in Cattaraugus County in the years 1925, 1926 and 1927 has been already discussed (3), and the mortality experience of 1928 and 1929 has not materially changed the general indications. It seems desirable, however, here, to summarize the conclusions already suggested and to bring the data up to date.

If no change in the trend of tuberculosis mortality as shown in figure 3 and table 10 had occurred subsequent to 1923, we would expect the trend

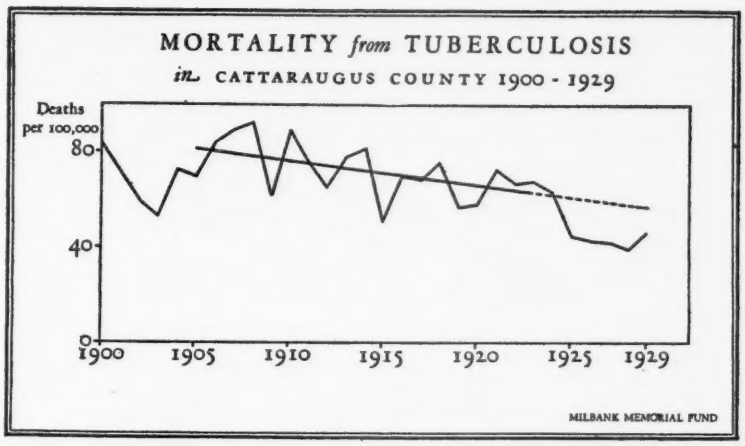

FIG. 3

values to decline from 61.2 ± 9.9 in 1925 to 57.1 ± 9.9 in 1929. As a matter of fact, the actual rates (45.3, 43.7, 42.1, 39.1 and 46.9 from 1925 to 1929) were from 10.2 to 32.7 per cent below the expected trend values. The rate of 46.9 for 1929 when considered alone is not a significant departure from the trend. However, if we can apply the theory of probability to such a problem as this, and assuming the independence of the events considered (and, statistically speaking, they may be so assumed), the occurrence of five successive rates as low as these may be judged as constituting a distinctly unique event in the history of tuberculosis in Cattaraugus County. The chances against its occurrence under the same conditions[9] as prevailed in 1905–1923 would be considerably more than one million to one.

[9] The occurrence of changes in economic and other conditions is referred to later.

Changes in the Age-Curve of Mortality: Of greater significance than the results of purely statistical tests is the fact that the decrease in the Cat-

TABLE 10

Deaths from tuberculosis (all forms) per 100,000 population in Cattaraugus County, 1900–1929

YEAR	DEATH RATE PER 100,000	YEAR	DEATH RATE PER 100,000
1900	83.5	1915	50.1
1901	71.1	1916	70.2
1902	58.7	1917	68.2
1903	52.5	1918	76.3
1904	72.6	1919	57.1
1905	69.5	1920	58.1
1906	83.9	1921	73.2
1907	89.4	1922	67.2
1908	92.5	1923	68.1
1909	61.6	1924	63.6
1910	89.2	1925	45.3
1911	76.2	1926	43.7
1912	65.0	1927	42.1
1913	77.9	1928	39.1
1914	81.8	1929	46.9

TABLE 11

Mortality from tuberculosis (1) (all forms) at different ages in Cattaraugus County and changes in mean annual mortality in 1916–1924 over 1925–1929

AGE	RATE PER 100,000		ACTUAL CHANGE IN RATE PER 100,000	RELATIVE CHANGE PER CENT
	1916–1924	1925–1929		
All ages	66.8	43.4	−23.4	−35.0
0– 4	14.5	19.4	+4.9	+33.8
5– 9	15.0	2.9	−12.1	−80.7
10–19	34.5	10.7	−23.8	−69.0
20–29	129.3	61.4	−67.9	−52.5
30–39	120.0	73.9	−46.1	−38.4
40–49	62.9	54.2	−8.7	−13.8
50–59	66.9	46.6	−20.3	−30.3
60–69	53.4	60.1	+6.7	+12.5
70 and over	63.8	91.7	+27.9	+43.7

(1) Excluding Indian deaths and nonresidents dying at J. N. Adam Memorial Hospital, Perrysburg.

taraugus County tuberculosis death-rate has taken place in the younger ages. This fact is clearly indicated by figure 4 and table 11 which compares the mean annual rates for 1916–1924 with those for 1925–1929 at

different ages. The rate among children under five years of age is slightly higher in the later period, but the numbers of deaths involved at this age are very few, averaging one per year in the earlier period and slightly more than one in the later period, and the change can hardly be considered significant. On the other hand, a very marked improvement in the mortality of children and adolescents has taken place, the decrease at ages 5–9 being 81 per cent and at ages 10–19, 69 per cent. The per-

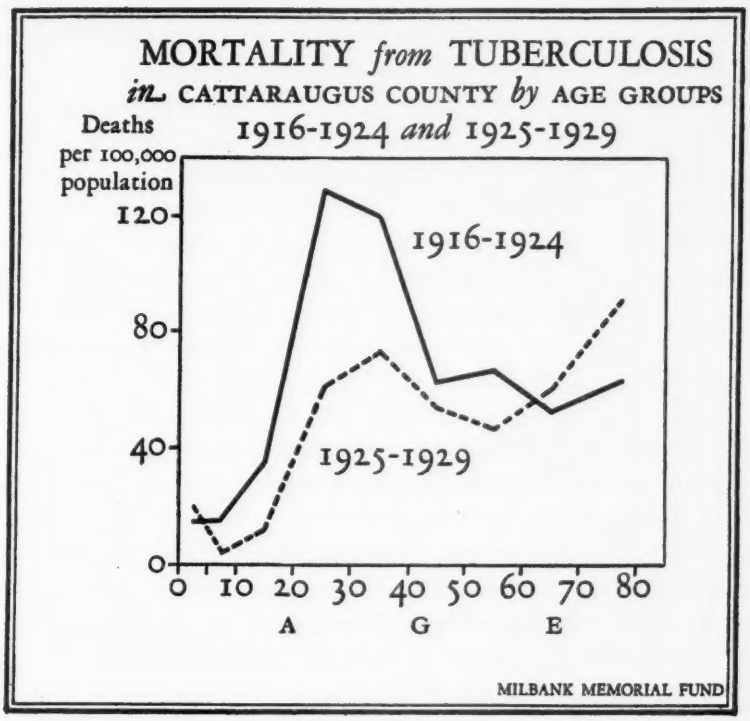

FIG. 4

centage decrease of 53 in the age period 20–29 is especially significant since at these ages the mortality reached its maximum in the previous period. With increasing age the relative decline diminishes until, at 60 years and over, some increase is indicated.

These foregoing indications as to mortality from tuberculosis, however, are arrived at by purely statistical analysis of the data as recorded; before they can be discussed from the point of view of their real significance as revealing the degree of success attained by the antituberculosis adminis-

tration or of their implications as to changes in procedure, certain other facts and considerations should be taken into account, as follows:

(*1*) *Accuracy of the Mortality Record:* The first consideration naturally concerns itself with the accuracy and appropriateness of the data recorded, since it is well known that mortality records are subject to certain statistical procedures, and are affected to a considerable extent, because of the small numbers involved in the present instance, by tendencies and differences in opinion.

In the first place, the factor of residence is of great importance in considering the mortality from tuberculosis within a specific area. Logically the deaths from tuberculosis should be allocated to the place in which the persons who died from the disease contracted it. For the mortality data presented in this study, a partial correction for residence has been made by excluding deaths of Buffalo residents occurring at the J. N. Adam Memorial Hospital, Perrysburg. It is impossible to make a complete correction, since information is not always available for residents of Cattaraugus County dying outside of New York State. However, for the years 1926, 1927 and 1928, the resident tuberculosis mortality (excluding Indian deaths) in Cattaraugus was 46.4, 42.0 and 45.8, compared with the recorded rates 43.7, 42.1 and 39.1 (4). The resident rates are slightly higher, with the exception of 1927, than the recorded rates. However, in the correction for residence made by Dr. DePorte, the deaths of residents of other states cannot be excluded except for 1928. Since Cattaraugus County is situated just north of a section of Pennsylvania, residents of that state seek hospitalization in the County, and the following deaths of Pennsylvania residents were recorded in Cattaraugus County: one in 1926 and two in 1927. On the other hand, one death among Cattaraugus residents in other states occurred in each of these years. This indicates that there is a fair balance between the partially corrected and resident tuberculosis mortality.

In the second place, there are several factors inherent in an intensive antituberculosis program which may tend to exaggerate the tuberculosis mortality rate. Occasionally, persons suffering from chronic illness have been diagnosed as having arrested tuberculosis (chronic fibroid type); the fact that the diagnosis of tuberculosis has at some time been made results in tuberculosis being recorded on the death certificate as a contributory cause of death and, according to the procedure prescribed by the Federal Bureau of the Census, such deaths are arbitrarily assigned to tuberculosis rather than to the disease which was the immediate cause

of illness and the actual cause of death. The following table (table 12) shows that during the period 1926–1929 from three to five deaths in each year fall in this category. These deaths, though few in number, are an important factor in an area where the death-rate is based on from 30 to 35 deaths annually.

Another factor affecting the tuberculosis mortality unfavorably is that of doubtful diagnosis. As shown in table 12, from one to four deaths annually during the period 1926–1929 attributed to tuberculosis may be considered in this classification.

Thus it appears quite probable that the recorded mortality from the disease has already been somewhat exaggerated by existing statistical and diagnostic procedures, and, unless such procedures are changed, this exaggeration will tend to increase rather than to decrease or to remain constant.

TABLE 12

Tuberculosis deaths recorded in Cattaraugus County and number which, for specified reasons, are unaffected by the tuberculosis program, 1926–1929

YEAR	TOTAL DEATHS ASCRIBED TO TUBERCULOSIS	TUBERCULOSIS PRESENT BUT NOT CAUSE OF DEATH	DIAGNOSIS OF TUBERCULOSIS DOUBTFUL	TOTAL MINUS DEATHS WHERE DIAGNOSIS DOUBTFUL AND TUBERCULOSIS NOT CAUSE OF DEATH
1926	32	4	1	27
1927	31	3	1	26
1928	29	3	3	23
1929	35	5	4	26

(2) *Possible Effects of Economic Changes:* In spite of this probable exaggeration, a statistically significant decline in the tuberculosis death-rate has occurred. Quite aside from the evidence on case-finding and supervision already summarized from the records, consideration should be given to the possibility that factors, other than those implied by a progressive tuberculosis administration, may have been responsible for this decline in mortality.

So far as we know, no marked change in the ordinary conditions that affect the tuberculosis death-rate has occurred in Cattaraugus County in the seven years 1923–1929. We have no evidence that the character of the population has altered significantly with respect to sex, age, occupation or race stock in this short time. A somewhat detailed tabulation of the 1925 census of population shows that its sex, age and nativity distribution was not materially different from that ascertained by the

1920 census, and the agricultural census and reports do not indicate that any marked change in occupations took place. Since major fluctuations in economic conditions in certain circumstances ordinarily tend to show some inverse correlation with major variations from the trend of the tuberculosis death-rate over a long period of years, the possibility ought to be considered that the recent decline in the rate in Cattaraugus County might be associated with an improvement in economic conditions. Using the index of prices of agricultural products, which is probably the best index of rural economic conditions, we find that since 1924 there has been some improvement in agricultural conditions in that section of the State in which Cattaraugus is located, the index of prices having risen from 120 (taking 1915 as 100) in 1921–1924 to 153 in 1928. But this apparent correlation of rise in the price index of 32 per cent with a decline in the tuberculosis death-rate of 41 per cent in the same period cannot be accepted as indicating a causal relationship in view of the fact that prior to 1924, when the fluctuations in economic conditions were much more pronounced, the price index ranging from 100 to 196, no corresponding variation occurred in the tuberculosis death-rate. The general conclusion is that a close association of variations in tuberculosis mortality and in prosperity cannot be predicated in a rural community such as Cattaraugus County.

6. SUMMARY AND DISCUSSION

An attempt has been made in this paper to measure the results of the antituberculosis activities of the health department in a rural area, Cattaraugus County, New York, during the period 1923–1929.

The method of measurement which has been used was to compare the situation after the antituberculosis activities were put into operation with the situation which existed before these activities had been developed. In other words, the comparison was a time comparison, an "experimental" period being contrasted with a "control" period. This study is limited to this method of measurement for the reason that suitable data are not yet available for comparing the results in Cattaraugus County with the results in other areas where a contrast would be afforded in the extent and character of antituberculosis work.

The data used were the clinical, nursing and mortality records as they were made in the ordinary course of administrative practice. So far as the nursing and clinical records are concerned, we have, as stated in the outset, accepted them as they were, being satisfied that, whatever

lacunae they presented, they were made according to the "best knowledge and belief" of persons whose honesty cannot be questioned. The accuracy and appropriateness of the mortality records were considered with the following results: (1) from the point of view of residence of decedents, the deaths from tuberculosis among nonresidents in Cattaraugus County appeared to balance the deaths of Cattaraugus County residents elsewhere; (2) the mortality rate from tuberculosis in Cattaraugus County apparently is somewhat exaggerated by reason of statistical procedure in classification according to cause of death and by an increasing tendency on the part of physicians to enter tuberculosis on the death-certificate as a cause of death.

The results of this attempt to measure the effectiveness of the antituberculosis activities so far in Cattaraugus County may be summarized briefly as follows: The evidence afforded by the records of cases strongly points to the conclusion that the tuberculosis administration already has been effective within certain limits. The development of facilities for discovery, care and supervision of tuberculosis cases has resulted in (1) an improvement in case-finding activities as shown by an increase in the number of active cases under supervision, and by the number of minimal cases discovered; (2) a reduction in the fatality of supervised active cases which has manifested itself in a marked decline in the mortality of children and adolescents. The gross result of this reduction in mortality is seen in a drop in the death-rate from tuberculosis during the past 5 years which is statistically significant in itself.

It should be realized fully that the time has not yet come for a full appraisal of the *ultimate* results of this experiment in rural health work. This is obviously true for several reasons. One is that childhood and minimal cases are just being brought under supervision and the effect of this type of preventive work cannot be seen until several years have elapsed. Another is that the effect of public-health education, especially in tuberculosis prevention and care, is not instantaneous but cumulative. The *immediate* results, so far as can be reflected in mortality experience, of necessity are confined largely to the prolongation of the lives of cases that can respond to supervision and sanatorium care.

A discussion of even the immediate results is not complete, however, without reference to the fact that the tuberculosis death-rate has stayed on practically the same level since 1925. The pertinent question naturally arises: To what is this failure to maintain a further decline due? Is it due entirely to an accumulation of deaths of moribund cases?

Were any of the deaths not under supervision of physicians, or of the health department, or of both? How much of the mortality occurred among persons who failed to coöperate with physicians or with the health department? To what extent were these fatal cases not reported promptly to the health department by the physicians and thus did not secure the benefit of the antituberculosis facilities?

No precise judgment can be made of the possible effect upon the death-rate by an unusual accumulation of moribund cases. For even if we assume that the particular individuals regarded as a moribund group could be identified positively, their number in this instance is too small to warrant any dependable estimate of their expectation of life under one set of conditions or another. Yet simple reasoning in arithmetic leads one to expect some temporary retardation in a declining mortality rate by reason of the postponement of the deaths of a specific moiety of the cases beyond the time they might have been expected, under usual conditions, to die. There is every reason to believe that such a special moiety was created by the introduction of better methods of tuberculosis control, but exactly how large it is or exactly how long it will last, is neither statistically predictable nor certain from the point of view of clinical prognosis. The facts that of the 127 deaths occurring in 1926–1929, 22, or 17 per cent, were of cases that had been under observation three or more years, and 29 more, or 23 per cent, had been under observation from one to three years, as shown in table 9, may be suggestive. Further experience must be awaited before a clearer anwer can be sought.

More definite, although only partially complete, answers to the other questions raised, can be made from a study of the rather careful sociomedical histories secured by Dr. Korns on all deaths that were officially ascribed to tuberculosis in the County in 1928–1929.[10] In these two years 64 deaths were so ascribed. Of this number 8 were definitely of persons who were not residents of Cattaraugus County or were of residents of Buffalo who took up residence in Cattaraugus County after treatment at Perrysburg; these 8 deaths may be subtracted from the 64 as not being true liabilities upon Cattaraugus County. In addition, there were 7 deaths for which the diagnosis of tuberculosis was considered doubtful by the Bureau of Tuberculosis; these also may be subtracted. We have

[10] Sociomedical histories of tuberculosis deaths were started in 1925 by Dr. Jensen. The data for 1928–1929 only have been used since only records compiled by one person are comparable in all details.

left, therefore, 49 tuberculosis deaths of Cattaraugus residents for consideration.

Now, of these 49 deaths, 26 occurred among patients who had been under supervision of the health department with the coöperation of the physician for a period of not less than six months. The remaining 23 deaths suggest some rather interesting avenues of inquiry from the point of view of more complete tuberculosis control since they were not under supervision.

Considering these 23 deaths, not less than 6 occurred among patients who refused to coöperate either with the physicians or the health department, after repeated efforts were made to secure coöperation. One of these cases had availed herself of the services of an osteopath and another of the services of a chiropractor. Whether or not some other method of approach on the part of the physicians or the public-health nurse or other types of health-worker might have brought about a different result it is impossible to say; the fact remains that the usual efforts were made to bring them under supervision for treatment. In addition to these 6 deaths, there were 6 other deaths which were not known to any physician, so far as can be ascertained, or to the health department for longer than a month before death. While these deaths may be ascribed to the failure of the patient or of his family or friends to avail themselves of the services of the health department and physicians, the fact must be faced that the existing methods of finding these cases or of stimulating these cases to discover themselves were ineffective. After careful scrutiny of the available information, it seems true that 9 deaths were of cases which were attended for a considerable period of time by physicians who definitely failed to coöperate with the health department. Of these 9, two were patients upon whom laboratory tests showed positive sputum but the attending physician refused to accept the diagnosis or report the case. The remaining 7 had been observed by physicians from $1\frac{1}{2}$ years to 5 years, but were reported much less than a year before death and were unknown to the health department until the report was made. In addition to the foregoing, there were 2 deaths for which there was record of inadequate service on the part of the health department.[11]

[11] In one of these cases known to be a contact, no tuberculin test or X-ray was made and the patient was declared to be without manifest tuberculosis upon clinical examination. No "follow-up" of this case was made in spite of the fact that both the brother and the father of the case had recently died from the disease; a diagnosis was made only four months prior to death. The other case was that of the father of two boys who had died from tuberculosis and of a girl who had had the disease, no further inquiry having been made into this case until it was found in a dying condition.

In summing up this experience, it seems fair to say that of the 49 deaths from tuberculosis among Cattaraugus County residents, 23, approximately half, occurred among persons who had not received any supervision from the health department. Of these, 9 may be ascribed to the failure on the part of the physician to coöperate with the health department and 12 were either entirely unknown to physicians or the health department or refused to coöperate. The indication seems clear that, if the same decrease in mortality as occurred among the cases under supervision is to be achieved among such cases as these, some further improvement in the case-finding machinery and in the coöperation of the private physicians is necessary.

This fact has been fully realized by the County Health Department and its advisors, and already an experimental project for developing methods of more intensive search for cases, particularly among contacts and school children, has been begun in Cattaraugus County. This project is closely coördinated with an epidemiological study of tuberculosis that is now under way.

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A STUDY IN BLOOD GROUPS

I. TUBERCULOSIS

K. T. SASANO[1]

Isohaemagglutinins were demonstrated in human serum by Landsteiner in 1906. The investigation of Jansky, 1907, and of Moss, 1910, established the presence of four distinct blood groups. Their observations were later confirmed by Hektoen and Ottenberg. Since that time much has been written on the subject of the blood groups in various diseases. McQuarrel (1) showed that 70 per cent of all cases of eclampsia occurred in cases in which there was an interagglutination between the blood of the mother and the infant. Rosling (2) in his study of diphtheria found more postdiphtheritic paralysis in group O than in group A. Of his 158 cases of psoriasis Poehlmann (3) found 55.5 per cent in group O, 29.1 per cent in group A, 12 per cent in group B and 3.2 per cent in group AB. Chominskiji and Scheustova (4) found a preponderance of group A in endogenous psychosis. The majority of writers however state that there is no specificity of blood group in any disease. Diamantopoulos (5) did not find any connection between the blood groups and the disease incidence. Meyer (6) in his study of blood groups in mental diseases found no particular psychosis showing preference for any particular blood group. Kraus and Medvei (7) found that the distribution of blood groups among their 100 hyperthyroid patients was about the same as in the normal controls. Their investigation was undertaken to determine the validity of the claim of Hermanns and Kronberg who found that 27 out of 28 cases of hyperthyroidism occurred in the same blood group. Lemke (8) did not find a marked deviation of blood groups from the normal distribution among the asthenic or tuberculous groups. Weidemann and Katkin (9) found no blood group predisposition in leprosy. Lekint and Troltzsch (10) found the blood-group determination valueless in differential diagnosis but very important in blood transfusion, tissue transplantation and malarial inoculation. Recently Parr (11) reviewed the conflicting reports of

[1] The Hegeman Memorial Laboratory of the Metropolitan Life Insurance Company Sanatorium, Mt. McGregor, New York.

various investigators and presented the results of his own study of 346 tuberculous patients and 944 tuberculin-tested inhabitants in Syria. In concluding his article he states that he "cannot support the contention that there is any relation between susceptibility to tuberculosis and any one blood group. Similarly no resistance to tuberculosis could be demonstrated for any one of the blood groups." On the other hand Alperin, Kallabis, Swider and Kon found that patients belonging to blood group A were more susceptible to tuberculosis while those belonging to group O were more resistant, as shown by Parr in table 1.

TABLE 1

Summary of work done on the relationship of clinical tuberculosis to blood groups

WORKERS AND REFERENCES	CASES	CONCLUSIONS
Hiersxfeld and Halber (*Zeitschr. f. Immunitätsf., 1926, xlviii, 37*)	300	Negative
Alperin (*Beitr z. Klin. d. Tuberc., 1926, lxiv, 500*)	515	Susceptibility in A
Hollo and Lenard (*Ibid., 1926, lxiv, 513*)	200	Negative
Streng and Ryti (*Acta Soc. Med. Finnicae Duodecim., 1927, viii, 1*)	828	Negative
Raphael, Searl and Horan (*Arch. Int. Med., 1927, xl, 382*)	400	Negative
Kallabis (*Beitr. z. Klin. d. Tuberc., 1927, lxvi, 391*)	515	Susceptibility in A
Sale (*Tubercolosi, 1927, xix, 181*)	200	Negative
Connerth (*Ztschr. f. Tuberk., 1927, xlviii, 140*)	667	Negative
Schmitt (*Deutsch. med. Wchnschr., 1928, liv, 2019*)	564	Negative
Koch and Wilckens (cited by Schmitt)	1100	Negative
Swider and Kon (*Compt. Rend. Soc. Biol., 1928, xcviii, 385*)	600	Susceptibility in A
Ernst (*Klin. Wchnschr., 1928, vii, 1036*)	200	Negative
Parr (*Jour. Prev. Med., 1929, iii, 240*)	346	Negative

The purpose of this investigation was to determine: first, the percentages of the different blood groups of the patients admitted to this sanatorium; second, the changeability of blood groups; third, the specificity of blood groups in various diseases; and fourth, the response to treatment of tuberculous patients belonging to different blood groups, especially groups A and O.

We began this work in 1927. More than 3,000 determinations of blood groups on 1,000 different individuals have been made. Four to ten examinations have been done in a number of cases. The reason for repeating the test was to ascertain whether there was any change in blood groups. Diamantopoulos (5) reported that in two cases of syphilis in women there was a change from group B to group O, during anti-

syphilitic treatment and that one case changed back to group B after four weeks. Thomsen (12) contradicted this statement, stating that there was not the slightest proof of a change in type. We have not found any change in blood grouping among the syphilitics during treatment here or among any other cases during the past three years, except

TABLE 2

Percentages of blood groups

NAMES	O	A	B	AB
von D. Herschfield	36	47	11	6
Moss	43	40	7	10
Olmstead	46	39	13	2
Karsner	46.2	42.4	8.3	3.1
Koeckert	43	38.5	12.5	6
Mt. McGregor: Total	42.7	40.3	12.4	4.6
Mt. McGregor: Nontuberculous	42.7	38.7	13.2	5.4
Mt. McGregor: Tuberculous	42.8	41.2	11.9	4.1

TABLE 3

Distribution of different diseases

DISEASES	O	A	B	AB	TOTAL
Tuberculosis	269	260	75	26	630
Duodenal ulcer	18	20	7	1	46
Syphilis	16	13	4	1	34
Thyroidism	9	10	3	1	23
Cardiacs	8	9	2	3	22
Arteriosclerosis	10	7	4		21
Arthritis	8	5	3	2	18
Bronchiectasis	6	7	3		16
Hyperpiesia	7	5	1	2	15
Diabetes	5	7		1	13
Nephritis	5	7		1	13
Chronic appendicitis	5	6			11
All other diseases (infrequent)	61	47	12	8	138
Total	427	403	124	46	1000
Diabetes (by Deegan)	125	22	12	3	162

in one case, that of a young tuberculous woman developing autohaemagglutinin during pregnancy. The test showed an apparent change in her blood group from B to AB. This change was due to the presence of the autohaemagglutinin, not to a change in isohaemagglutinin.

Our percentages of the different blood groups in all the cases we examined did not differ materially from the percentages given in the literature, as shown in table 2. Our figures failed to show anything of importance relative to the specificity of blood groups to disease, as shown in table 3.

Of the 1,000 cases, 427 were in group O, 403 in group A, 124 in group B and 46 in group AB. The 370 nontuberculous cases were divided as follows: 42.7 per cent in group O, 38.7 per cent in group A, 13.2 per cent in group B and 5.4 per cent in group AB. Of the 630 tuberculous cases 42.8 per cent belonged to group O, 41.2 per cent to group A, 11.9 per cent to group B and 4.1 per cent to group AB, as shown in table 2. According to these figures, the percentages of blood groups of the tuberculous do not differ greatly from those of the nontuberculous, except for

TABLE 4

Comparative percentages in tuberculosis

	O	A	B	AB
Total on admission	42.8	41.2	11.9	4.1
Bed patients, June, 1929	48	34	16	2
In bed over one year	53	26	19	2
Bed patients in December, 1929	50.9	34	14.1	1
In bed over one year	63.6	24.2	12.2	
Deaths in past 3 years	9	4	3	

a slight increase in group A and a slight decrease in group B. From this one might infer that individuals belonging to group A are more susceptible to tuberculosis, but in following up these cases the figures are reversed. In the summer of 1929 a tabulation of all the tuberculous bed-patients revealed that 48 per cent belonged to group O, 34 per cent to group A, 16 per cent to group B and 2 per cent to group AB. At this time, of the patients who had been hospitalized over one year, 53 per cent belonged to group O, 26 per cent to group A, 19 per cent to group B and 2 per cent to group AB. In December, 1929, we studied all our tuberculous bed-patients again and found that 50.9 per cent belonged to group O, 34 per cent to group A, 14.1 per cent to group B and 1 per cent to group AB. Of the patients who had been hospitalized over one year, 63.6 per cent were in group O, 24.2 per cent in group A, and 12.2 per cent in group B. During the period of this investigation,

there occurred 9 deaths in group O, 4 in group A and 3 in group B, as shown in table 4.

Table 5 shows the blood-group distribution of the incipient (I), moderately advanced (MA) and far advanced (FA) cases of tuberculosis. There was a total of 630 tuberculous cases. Two hundred and sixty-nine patients belonged to group O. Of these, 112 (17.7 per cent) were

TABLE 5

Comparative tables of tuberculous cases

	O			A			B			AB		
Total admitted cases: 630	269 (42.8%)			260 (40.2%)			75 (11.9%)			26 (4.1%)		
	I	Ma	Fa	I	Ma	Fa	I	Ma	Fa	I	Ma	Fa
Number	112	103	54	108	106	46	31	27	17	10	7	9
Per cent	17.7	16.3	8.5	17.1	16.8	7.6	4.9	4.3	2.7	1.6	1.1	1.4
Patients now at sanatorium: 197	97 (49.2%)			69 (35%)			25 (12.8%)			6 (3%)		
Number	16	48	33	14	31	24	3	13	9	0	1	5
Per cent	8.3	24.4	16.7	7.1	15.7	12.2	1.5	6.6	4.5	0	0.5	2.5
Patients in sanatorium over 1 year: 76	38 (50%)			22 (29%)			14 (18.4%)			2 (2.6%)		
Number	5	18	15	2	8	12	1	9	4	0	0	2
Per cent	6.5	23.7	19.7	2.6	10.5	15.8	1.3	11.8	5.5	0	0	2.6
Present bed patients: 112	58 (52%)			36 (32%)			16 (14.2%)			2 (1.8%)		
Number	4	26	28	1	15	20	3	6	7	0	0	2
Per cent	3.6	23	25	0.9	13.4	18	2.7	5.3	6.3	0	0	1.8
Patients in sanatorium over 1 year: 45	25 (55.5%)			13 (28.8%)			5 (11.2%)			2 (4.5%)		
Number	4	9	12	1	4	8	1	2	2	0	0	2
Per cent	8.9	20	26.6	2.2	8.9	17.7	2.2	4.5	4.5	0	0	4.5

incipient, 103 (16.3 per cent) were moderately advanced, and 54 (8.5 per cent) were far advanced. Of 260 patients belonging to group A, 108 (17.1 per cent) were incipient, 106 (16.8 per cent) were moderately advanced, and 46 (7.6 per cent) were far advanced. Seventy-five patients were in group B. Thirty-one (4.9 per cent) of these were incipient, and 27 (4.3 per cent) were moderately advanced. Of 26 patients belonging to group AB, 10 (1.6 per cent) were incipient, 7 (1.1

per cent) were moderately advanced, and 9 (1.4 per cent) were far advanced. The relative percentage of incipient, moderately advanced and far-advanced cases at the time of admission corresponded fairly closely in groups O and A.

At present there are 197 tuberculous patients in the Sanatorium. Ninety-seven (49.2 per cent) belong to group O. Of these, 16 (8.3 per cent) are incipient, 48 (24.4 per cent) are moderately advanced, and 33 (16.7 per cent) are far advanced. Sixty-nine (35 per cent) are in group A. Among these, 14 (7.1 per cent) are incipient, 31 (15.7 per cent) are moderately advanced, and 24 (12.2 per cent) are far advanced. Of 25 (12.8 per cent) belonging to group B, 3 (1.5 per cent) are incipient, 13 (6.6 per cent) are moderately advanced, and 9 (4.5 per cent) are far-advanced. Six (3 per cent) belong to group AB. One (0.5 per cent) of these is moderately advanced and 5 (2.5 per cent) are far advanced.

Of the 197 tuberculous patients in the sanatorium at the present time, 76 have been hospitalized over one year. Of these, 38 (50 per cent) belong to group O. In this group 5 (6.5 per cent) are incipient, 18 (23.7 per cent) are moderately advanced, and 15 (19.7 per cent) are far-advanced. Of 22 (29 per cent) cases which are in group A, 2 (2.6 per cent) are incipient, 8 (10.5 per cent) are moderately advanced, and 12 (15.8 per cent) are far advanced. Fourteen (18.4 per cent) belong to group B. One (1.3 per cent) of these is incipient, 9 (11.8 per cent) are moderately advanced, and 4 (5.5 per cent) are far advanced. Two (2.6 per cent) are in group AB, and they are both far-advanced cases.

According to these figures the differences between the percentages of groups O and A at admission and after one year of hospitalization are not sufficiently striking to conclude that any blood group is more resistant to tuberculosis than another. The number of bed-patients and of far-advanced cases of tuberculosis is higher in group O than in group A and the greatest number of deaths has occurred in group O. The results of our study do not agree with the conclusions drawn by some authors that individuals who belong to group O are more resistant to tuberculous infection or that individuals who are in group A are more susceptible to this infection.

SUMMARY

The percentages of blood groups of 1,000 cases agree closely with those of Karsner and Koeckert.

In the past three years 3,082 tests on 1,000 individuals have not revealed any evidence of a change in the blood group of an individual.

We have not found any specificity of blood group for any particular disease.

There is no evidence of a greater resistance or susceptibility to tuberculosis in any one of the blood groups. The response to treatment appeared to be better among the tuberculous individuals in group A than among those in group O.

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STUDIES ON THE CALMETTE-GUÉRIN STRAIN OF THE TUBERCLE BACILLUS (BCG)[1]

I. THE EFFECT IN VITRO OF ENVIRONMENT ON THE VIRULENCE OF BCG

K. T. SASANO AND E. M. MEDLAR

During the fall of 1928 we began a critical study of the *Bacillus Calmette-Guérin* strain of bovine tubercle bacillus which Professor Calmette of the Pasteur Institute in Paris has sponsored unreservedly as a sure protection against subsequent infection with the human tubercle bacillus. He has also maintained that this culture is innocuous and harmless, even when given in large doses to infants. In a recent article Calmette (1) has stated that BCG is a *virus fixé* and that no one has been able to increase its pathogenicity.

The investigations of Petroff and Branch (2) in this country and of Watson (3) in Canada do not support the claims of Calmette as to either the immunizing efficiency or the innocuity of *BCG*.

The culture of *BCG* which we have used in our experiments was originally obtained from W. H. Park of New York City in 1926. This culture has been grown continuously on bile-glycerine-potato medium as recommended by Calmette. The results of previous work done in this laboratory with this culture have been reported by King and Park (4). Their findings were largely confirmatory of the claims of Calmette, except that in one guinea pig progressive tuberculosis could be demonstrated.

We have repeated, on a smaller scale, the work of King and Park. Inoculation of rabbits and guinea pigs with as much as 20 mgm. of the *BCG* grown constantly on bile-glycerine-potato medium has failed to produce progressive tuberculosis and death of the animals. We have always obtained lesions in the guinea pig at the site of inoculation and in the regional lymph nodes. On several occasions tubercles were found in the spleen, liver and tracheobronchial lymph nodes. The finding of

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such lesions is of significance, as it demonstrates that the bacilli are not entirely localized at the site of inoculation. We have not as yet made an attempt to increase the virulence of the organism by repeated animal passage from these lesions.

The studies we wish to emphasize in this report are those on the effect, *in vitro*, of culture media upon the virulence of *BCG*. The purpose of our work was to attempt to establish in our culture media an environment, as far as nutritive substances were concerned, quite similar to that present in living tissues. By cultivating *BCG* on such a medium we felt that the bacillus might be better prepared to adjust itself to the environment of the living body. We have made no attempt to dissociate *BCG* by the colony method used by Petroff and Branch. Instead, we have taken a loopful of the growth on bile-glycerine-potato and transferred it directly to the various culture media with which we have been experimenting. If growth was successful on the new medium then subcultures were made on the same type of medium. After numerous experiments we chose the following medium as best suited for our purposes: Sauton's medium, adjusted to pH 7.2–7.4 just prior to inoculation, and with 10 per cent of normal unheated rabbit serum added just before inoculation of the medium.

The modified formula of Sauton's medium, as we used it, was as follows:

Dipotassium phosphate	0.5	gm.
Magnesium sulphate	0.5	gm.
Citric acid	2.0	gm.
Asparagin	4.0	gm.
Iron citrate (ammoniacal)	0.05	gm.
Glycerol	35	cc.
Distilled water to	1000	cc.

Neutralize the medium to pH 6.8 with sodium carbonate. Autoclave at 15 pounds pressure for 30 minutes.

We used normal rabbit serum fractionally sterilized at 56°C. in our first experiments. With this medium we obtained excellent growth of the bacilli and a moderate increase of virulence. We produced in rabbits a chronic progressive tuberculosis. However, we were not satisfied with the degree of virulence obtained, nor with the rapidity of return of virulence. Because of this we shifted to the use of fresh unheated normal rabbit serum and discontinued further experiments with the heated serum. With the unheated serum the growth of the organism was slow

at first, but the return of virulence was more rapid and the degree of virulence was greater. It would seem that fractionally sterilizing the serum altered it in some way that retarded somewhat the increase of virulence. A control flask of medium was always used. This control contained the same amount of the same lot of unheated serum that was used in the flasks inoculated with tubercle bacilli.

When the culture was transferred from the bile-glycerine-potato medium to the Sauton serum medium it was found that the pH greatly affected the growth of the bacilli. If the pH approximated 6.8 growth was rapid and luxuriant, and closely resembled in gross the growth on the bile-glycerine-potato medium. Under such circumstances the virulence was not much increased. If the pH was above 8.0 no growth occurred. When the pH was adjusted between pH 7.2 and 7.4 growth was slow at first. Subsequent transplants grew more rapidly and the gross appearance of the culture began to change. Because of the alteration in the appearance of the growth the medium adjusted to pH 7.2 to 7.4 was adopted for our subsequent studies. Subcultures were made every four weeks. Rabbits were inoculated intravenously at the time of subculture.

The fourth subculture on this medium grew rapidly and the gross appearance of the culture was different. Instead of a compact, tenacious, rough growth the bacteria had spread out over the entire surface of the medium as a thin veil which was easily broken up. This gross characteristic became more marked with subsequent transplants until eventually the growth was veil-like from the start.

Another characteristic observed was that a homogeneous suspension was easily obtained with this veil-like growth, whereas such a suspension was difficult to obtain with the growth on the bile-glycerine-potato medium.

At the time the study was begun rabbits were inoculated intravenously with 20 mgm. of *BCG* from the bile-glycerine-potato medium. These rabbits were allowed to live for a year and were then killed. They had never appeared ill and were in good physical condition at the time they were killed. No gross evidence of tuberculosis was found at necropsy. Microscopic examination of the tissue showed rare giant cells and small tubercles in the lungs, spleen and liver, and small collections of lymphocytes in the lungs and liver. No tubercle bacilli could be demonstrated in the tissues after prolonged search. Similar findings were observed in rabbits intravenously inoculated at dates prior to the be-

TABLE 1

Results of intravenous inoculation of various subcultures

SUBCULTURE	NUMBER OF RABBITS INOCULATED	INTRAVENOUS INOCULATION	RESULT	GROSS PATHOLOGY	MICROSCOPIC PATHOLOGY
		mgm.			
3	2	1	D. 30 d.	Ext. gen. Tb.	Acute tuberculosis. Bacilli numerous.
			D. 50 d.	Ext. gen. Tb.	Acute tuberculosis. Bacilli numerous.
4	2	1	D. 30 d.	Ext. gen. Tb.	Acute tuberculosis. Bacilli numerous.
			D. 40 d.	Ext. gen. Tb.	Acute tuberculosis. Bacilli numerous.
5	2	1	D. 13 d.	Ext. gen. Tb.	Lesions mostly abscesses. Bacilli very numerous.
			D. 20 d.	Ext. gen. Tb.	Lesions mostly abscesses. Bacilli very numerous.
6	2	1	D. 11 d.	Ext. gen. Tb. (ruptured colon)	Lesions mostly abscesses. Bacilli very numerous.
			D. 22 d.	Ext. gen. Tb.	Lesions mostly abscesses. Bacilli very numerous.
7	2	1	D. 21 d.	Ext. gen. Tb.	Lesions mostly abscesses. Bacilli very numerous.
			D. 22 d.	Ext. gen. Tb.	Lesions mostly abscesses. Bacilli very numerous.
8	1	0.1	D. 30 d.	Ext. gen. Tb.	Lesions mostly abscesses. Bacilli very numerous.
Control	2	20	K. 1 yr.	No Tb.	Rare mononuclear tubercle and giant cell in lung and spleen. Collections of lymphocytes in lung and liver. No bacilli demonstrated.

ginning of our present study. These observations establish the non-pathogenicity of the culture up to the time it was transferred to the Sauton serum medium.

Table 1 gives the data on the rabbits inoculated with the various subcultures on the serum medium. It will be noted that death occurred at an earlier date with the later subcultures; also, that with subculture no. 8 the virulence had been increased to such an extent that with one-tenth of the dosage death occurred as soon as it did with subculture no. 3.

The animals all showed extensive tuberculosis with the greatest involvement in the lungs. In several instances the lungs exhibited a tuberculous pneumonia which practically solidified the organ. The liver was usually uninvolved, as far as the gross pathological examination revealed. The spleen was always moderately enlarged and showed few to many tubercles. The kidneys were usually slightly involved. The bone-marrow appeared hyperplastic but showed no gross tubercles. Occasionally tubercles were present in the heart muscle and in the intestinal wall. In one instance there was a large tuberculous lesion of the stomach wall. The joints were not involved. The genital organs were normal.

The microscopic pathological changes of the rabbits dying from twelve to twenty-two days showed a very acute infection. The lungs revealed many abscesses composed very largely of neutrophiles. Mononuclear tubercles were rare; giant cells were very scarce. Caseation was very slight. In sections stained with carbol-fuchsin the bacilli were so numerous in the majority of instances that the lesions appeared red under the low power of the microscope. The lesions in the spleen and kidney were more typical of the accepted pathological picture of tuberculosis. Tubercles were commonly found in small numbers in the bone-marrow, and in these lesions tubercle bacilli were few in number. Tuberculous lesions were not frequent in the liver.

We took a small portion of the spleen from the rabbit dying in fifty days from subculture no. 3, emulsified it, and injected the emulsion intravenously into a normal rabbit. A smear of the emulsion stained for tubercle bacilli showed very few bacilli present. This rabbit died in two months with generalized tuberculosis. Subsequent transfers of a similar nature in this series have given the following results: Transfer no. 2 died in four months; transfer no. 3 died in three months; transfer no. 4 died in four months; transfer no. 5 died in seven weeks; and transfer no. 6 is alive at the end of three months, but it is emaciated.

We have been able to cause death with extensive generalized tuberculosis in five successive generations by direct animal passage from rabbit no. 3. The gross and microscopic pathological changes in the animals of this series have been those of a more chronic progressive tuberculosis with extensive caseation, giant cells, and areas of calcification with very little tendency to repair. Tubercle bacilli were very numerous in the acute tuberculous abscesses and very few in the areas of old caseation. There has been considerable variation in the length of life of these animals. This can be accounted for by the variation in the dosage of tubercle bacilli. In some instances smears from the splenic emulsion showed very few tubercle bacilli, while in other instances one or more bacilli were present in every oil-immersion field. It is of significance that the virulence of the tubercle bacillus had increased to such an extent that a few bacilli were capable of causing progressive tuberculosis and death consistently.

We have inoculated guinea pigs subcutaneously and calves intravenously with subcultures subsequent to transfer no. 8 and have consistently caused death in these animals. Guinea pigs inoculated with 0.02 mgm. die within sixty days from generalized tuberculosis. Two calves inoculated with 3 mgm. intravenously died in twenty-four days, and a calf similarly inoculated with 0.8 mgm. died in thirty-four days.

DISCUSSION

The advisability of administering living microörganisms, which have pathogenic potentialities, to human beings as a vaccine is, we feel, open to question. If living microörganisms are to be used as a vaccine one must be fully aware of the conditions under which the bacteria should not be grown, as well as those under which the pathogenic properties are suppressed to a point where they are relatively harmless. The data presented above are given with the purpose of emphasizing the potential pathogenic proclivities of *BCG*. We accept Calmette's claim that the pathogenicity of *BCG* has been greatly curbed by growing it for a long period of years on bile-glycerine-potato medium. We do believe, however, that Calmette's statement that *BCG* is a *virus fixé* may lead many workers to believe that it makes very little difference under what conditions the organism is grown. It is very evident from our experiments that cultural environment has a profound effect upon the virulence of *BCG*.

Our experiments convince us that it is possible to greatly enhance the virulence of *BCG* if the culture is grown in a suitable environment. We do not feel that we have determined the only environment in which *BCG* may become virulent. To obtain good growth of the original *BCG* culture in the new environment was difficult. It has been our experience that it is essential to have the pH adjusted between 7.2 and 7.4. This has necessitated the titration of Sauton's medium just prior to the addition of the fresh rabbit serum and to the transfer of the culture, for we have found the medium to be rather unstable. Fresh unheated rabbit serum appears to be essential if the virulence is to be *rapidly* increased. Here the difficulty of obtaining sterile serum was encountered, but nonsterile serum was the exception when careful technique and healthy rabbits were used.

In spite of the vast amount of research work that has been done, very little is yet known relative to the conditions essential to the establishment and maintenance of the virulence of pathogenic microörganisms. This is especially true of the tubercle bacillus. Environment undoubtedly is the deciding issue, but the factors necessary to produce the proper environment are largely unknown. Proper temperature and accurate adjustment of the pH of the medium are essential. Normal unheated rabbit serum apparently contains a substance or substances very favorable for the rapid development of virulence.

BCG, when grown under the environment which we succeeded in establishing, has evidenced a virulence greater than any other culture of tubercle bacillus we have had in our laboratory. For over six months since the return of virulence we have kept the culture on Petroff's egg medium. The virulence is still present, but it is not as potent as when first cultured.

Another fact of great importance is that our altered culture of *BCG* became equally pathogenic for rabbits, guinea pigs and cattle.

Our work substantiates the observations of Petroff on the "dissociation" of *BCG*. We have not used the same method but our end-results are similar. There is no question but that the gross appearance of virulent and of nonvirulent cultures is different. The virulent culture is smooth, veil-like and colorless, and is easily emulsified. The culture of low virulence is rough, compact and often chromogenic, and is emulsified with difficulty.

In our work we have purposely taken the original culture without any attempt to isolate different types of colony. There can be no

question of contamination in our method, nor do we hesitate to discard completely the charge of contamination in Petroff's investigations. We have succeeded in altering the original *BCG* culture in its gross appearance and in its virulence without resorting to isolation of single colonies.

Since it is possible to bring about such a marked alteration of *BCG in vitro*, and since so little is known concerning the factors that enhance or retard the pathogenicity of the tubercle bacillus, it would seem essential to use great caution in any application of *BCG* as a prophylactic vaccine against tuberculosis; particularly important is the selection of culture medium to be used for the cultivation of *BCG*. While Calmette's observations point, so far, to the innocuousness of the vaccine, one must not lose sight of the fact that all control over the tubercle bacillus and its activities is relinquished once it gains access to the tissues.

The sum and substance of our investigations tends to prove that *BCG* is not a *virus fixé*, and that its stability depends entirely upon its environment.

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BENIGN ACUTE PULMONARY TUBERCULOSIS[1]

GEORGE G. ORNSTEIN, DAVID ULMAR AND EDGAR LEON DITTLER

In the course of our work in pulmonary diseases it has been our lot in both private and institutional practice to observe cases of pulmonary tuberculosis which did not run the chronic course usually associated with acid-fast infection of the lungs. Our attention was first called to this type of disease by the fact that many of our so called advanced stages of tuberculosis tended to clear up very rapidly and to disappear completely without leaving any trace of their former presence. Within six weeks to a few months all evidence of the lesion would have disappeared. Whereas formerly the X-ray showed extensive lobar shadowing, now the film was perfectly clear. These observations aroused our curiosity and started us on our present investigation, the results of which will be summarized below.

The conception of tuberculosis as an acute disease is not new. The French School were probably the originators of the idea, there being mention made as early as 1829. Grancher (1) in 1877 described a *splenopneumonie tuberculeuse* but his ideas do not seem clear. It is really not till the present century that any definite views have been published as to the acute form of tuberculosis. Thus Bard (2) in 1901 in his classification viewed this *splenopneumonie* of Grancher as a form of the true caseous pneumonia.

In a lecture on the curability of acute phthisis Anderson (3) in 1890 said that its prognosis was not gloomy. He cited the case of a man who was well after an illness of twenty-eight days. In 1906 West (4) divided acute phthisis into two groups. He stated that "both are attended with extensive inflammatory consolidation but in one, consolidation itself is tuberculous, for tubercle bacilli are found in the alveolar contents, and it rapidly caseates; in the other, the consolidation is simply inflammatory and not really tubercular. It may resolve and then disappear." Heller (5) in 1904 and Hedinger (6) in 1906 published the autopsy reports of extensive acute lobar tuberculosis where the process had not extended to caseation. It was their idea, however, that if the patients had lived

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long enough caseation would have occurred. In 1909 Gerhardt (7) cited an acute case with recovery in 13 weeks and complete well-being one year later. He stressed A. Fraenkel's point of the resorbability in the gelatinous areas where no tubercle bacilli were to be found. In the following years Bezançon and Braun (8) and Mohr-Stähelin (9) pointed to the disappearance of acute infiltrations. In this country it was Wessler (10) (11) who first published the roentgenological disappearance of large consolidations, but he did not conceive the lesion to be benign for he speaks of these patients having "wavered on the brink of death." In 1925 Redeker (12) described the disappearance in children of extensive tuberculous processes in a short time. A similar process in adults was described in 1926 by Fassbender (13). Thirty-one cases were cited. Fleischner (14) in 1925 described the rapid disappearance of exudative processes, which on X-ray could not be differentiated from the nonresorbable caseous pneumonic type. In 1926 Sergent and Durand (15) stated there was a lobar form of tuberculosis which resorbs completely. Rist (16) in 1916 and again in 1919 speaks of an acute form of tuberculosis which may recover rapidly. To continue with this review of the literature would be repetitious. The following men have contributed to the study of an acute form of tuberculosis: in 1920, Eliasberg and Neuland (17) (18); in 1921, St. Engel (19); in 1922 Assmann (20), Jaquerod (21), Armand-Delille (22), and Klinkert (23); in 1923 Schurmann (24), Harms (25), Piquet and Giraud (26), and Rennenbaum (27); in 1926, Ulrici (28) (29), Bacmeister (30), Ickert (31) and Lydtin (32) (33); in 1927 Crecelius (34), Lindig (35), Neumann (36), Romberg (37) and Jacob (38); in 1928, Brecke (39), Alexander (40) and Mastbaum (41); in 1929, McPhedran.

SYMPTOMATOLOGY

The symptoms presented by patients with this type of pathological involvement are typically very slight. Usually the disease is ushered in by what is described as an ordinary every-day cold. Following a period of perfect health, the patient, generally a young adult in our series, although this type of reaction may occur at any age, notices the onset of a slight cough. This cough, never severe, within a few days to a week diminishes, so that by the end of a week or so the patient is coughing practically not at all. Coincident with the onset of the cough there is a scanty amount of sputum. This expectoration lasts but a few days and then disappears. This fact is of great practical significance.

If tubercle bacilli are to be found in the sputum, they must be searched for within the first few days of the onset of the disease. Subsequent examinations may be made on ordinary saliva furnished by an obliging patient who is unable to raise any sputum. This question of the presence of tubercle bacilli will be discussed more fully in the section on pathology and aetiology.

At the onset of the attack, the patient may feel a trifle below par. This feeling of malaise and lassitude may be no greater than that associated with an ordinary common cold. It soon disappears, and with the subsidence of the cough and expectoration the patient feels perfectly well. The entire symptom-picture usually lasts no longer than a few days to a few weeks, and, as far as the patient himself is concerned, he is willing to consider himself cured by the end of this short period.

In our description of the symptomatology there is one finding which has not been mentioned up to now. When present it is of very great significance and serves to differentiate this type of pulmonary infection from that found in the ordinary common cold. We refer to the symptom haemoptysis. Blood-spitting has been noted in 43 per cent of our series. When present, it occurs at the very onset of the disease. It may vary in amount from merely blood-streaked sputum to copious haemorrhage of a pint or more. We know of no ordinary cold which produces this picture. When haemoptysis is associated with a slight cough and expectoration which soon disappear and leave the patient feeling perfectly fit, we are very suspicious of the presence of the acute benign form of tuberculosis. If the patient gives a history of recent contact with an open case of tuberculosis, our diagnosis is practically clinched. This last factor will be more fully discussed in the section on aetiology.

PHYSICAL SIGNS

The physical signs in this type of disease are surprisingly scant when one considers the extent of the pathological changes as revealed by the X-ray. Usually the breath-sounds over the involved area are markedly diminished; in fact, their intensity is diminished to such an extent that the quality of the breathing occasionally cannot be determined. When the type of respiratory murmur can be distinguished, it is usually found to be bronchovesicular. At the onset of the disease there may be a few fine high-pitched moist râles scattered over the involved area. These râles, never numerous, seldom coarse, usually fine and high-pitched, persist for a varying length of time. They may be present for but two

or three days and then completely disappear. In other cases, they may be heard for the duration of the pathological process. Sometimes there are a few scant sibilant or sonorous râles. Occasionally no râles are ever heard. There is one finding, however, which is fairly constant. Dulness on percussion can usually be obtained over the involved region, provided that the area is extensive enough and sufficiently close to the chest-wall to be revealed by this method of physical diagnosis. When one considers the exudative nature of the process one is not at a loss to explain the paucity of physical signs. The oedematous water-logged alveolar walls act as perfect felt-pad dampers and thus prevent the formation or transmission of breath-sounds or râles. The percussion note, however, is not influenced by this factor and is therefore dull.

X-RAY

Following upon a somewhat unimpressive history and very scant physical signs, the X-ray film is rather astounding. In full bloom the roentgenographic picture presents a dense homogeneous shadowing. This shadow may be of any size and may occupy any portion of the lung field. Frequently it involves an entire upper lobe, and when on the right side may have a sharp lower border at the level of the interlobar fissure between the upper and middle lobes. Occasionally the shadow is wedge-shaped, with the base toward the periphery of the lung field and the apex toward the hilum. Extensive as the X-ray shadowing may be, it is very rapid in making its appearance. One of our cases showed marked changes within four days. The first change to be noted is a diffuse haze and impairment of illumination over the involved area. This is followed by a rapid increase in the density of the shadow, until the typical homogeneous opacity is obtained.

Once the peak of the reaction has been reached and the process tends to resolve, the X-ray shadow tends to disappear. This it does in one of two different ways. The shadowing may gradually disappear by means of a uniform diminution of the density—a reversal of its formation. The more usual manner of disappearance is by means of an irregular absorption of the shadowing, leaving a mottled patchy appearance, exceedingly suggestive of cavitation. This absorption may even take place in such a manner that the entire centre of the shadow is absorbed, leaving a large area of high light which is usally diagnosed by the roentgenologist as a large cavity. At other times this irregular fade-out may, in the course of its resolution, present an appearance similar to the shadowing caused

by the chronic proliferative or acinonodous type of tuberculosis. Serial X-rays, however, often after a period of no longer than six weeks to a few months, show that the entire shadowing disappears, usually without leaving a trace. It is very important that these X-ray shadows be recognized during their stage of resolution. Frequently the patient is seen late in the course of the disease and only after the lesion has been discovered during routine flouroscopic examination. Unless one is cognizant of the peculiar irregular process of absorption of the shadow, the case may be diagnosed as advanced tuberculosis with cavity-formation. Gross damage, the result of misplaced therapy, can be done because of this simple error.

As indicated by the title of this paper, the course of this form of tuberculosis is acute in its onset, rapid in its course, and tends to resolve without leaving any trace of its former presence. The entire cycle of events from the onset to the completion of resolution may not last longer than from six to eight weeks. The treatment is merely rigid bed-rest.

AETIOLOGY AND PATHOLOGY

Concerning the pathology of this type of tuberculosis, very little is definitely known, for the simple reason that patients with this form of tuberculosis do not die but usually recover. Experiments are now being conducted to further study of this problem. Briefly our ideas on this subject can be stated as follows: Following the primary infection with the tubercle bacillus, the cells of the body become so altered that they react in an entirely different manner to any subsequent superinfection. This altered reaction assumes two different forms. One is a true immunity response, the reaction which prevents the spread and migration of the tubercle bacilli and results in the proliferative or fibroid process of healing. The other is a somewhat related reaction but nevertheless one which on superficial thought does not seem to be primarily defensive. This second type of reaction, the so called allergic or hypersensitivity reaction, a primarily exudative or serous reaction, is one which tends to result in injury to the cell. It seems to parallel the immunity reaction but not necessarily so. The whole process of immunity and allergy is very poorly understood at the present time. From a practical point of view, with our present state of knowledge, we can state that some individuals, highly sensitive to the tubercle-bacillus protein, react with a predominantly allergic response, while others seem to react to the same

stimulus by means of the immunity reaction with its resultant fibroid tuberculosis. It is our opinion that the type of reaction depends upon the relationship between the dosage and virulence of the superinfection and the reaction of the cells of the host; in other words, upon the relationship between the tubercle-bacillus protein and the threshold level of the body cells to allergic stimulation. If the threshold level is high, a comparatively large dose of bacilli will be required to produce the allergic reaction. On the other hand, a person who has a low threshold level, that is, a person who is very allergic, will react to a minute dose of tubercle bacilli with an intense allergic or serous exudative type of reaction. It will therefore be readily seen that if a person of this allergic type comes in contact with a small dose of tubercle bacilli, he will react with a sudden acute exudative reaction. If the same individual is then removed from the source of bacilli so that there will be no further dosage to cause permanent damage, then the acute exudative reaction will subside, the exudate will be absorbed, and no trace of the previous pathological changes will remain. This very briefly is what we consider to be the pathogenesis of the acute benign form of tuberculosis.

From this brief discussion it can be seen how significant becomes the history of contact with an open case of tuberculosis. An allergic individual inhales a dose of tubercle bacilli that has been sprayed out by a person with a positive sputum. The bacillary protein comes in contact with the highly sensitized lung tissue. A tremendous exudative reaction takes place,—practically similar to the tuberculin reaction (Koch phenomenon). There is a tremendous serous exudation into the alveolar walls and alveoli, a slight amount of fibrin, and just a few cells. The few bacilli which were the cause of reaction soon become "lost in the scuffle," so to speak, and eventually disintegrate and are destroyed. It is therefore difficult to find the bacilli in the sputum and after the first few days of the illness they are practically never seen. This is the type of reaction that is found when the dosage of bacilli is derived from an exogenous source. A similar picture may result when the germs are derived from an endogenous source, that is, when the organisms spill over from one part of the lung field and set up an exudative focus in some new area. There are also times when a tremendous exudative reaction takes place about an old proliferative focus. The exact pathogenesis of this reaction is not quite clear. One thing, however, is certain, and that is that allergic tissue has been stimulated to reaction by tubercle-bacillus protein. With the removal of the irritating stimulus or possibly a raising of the threshold

of stimulation, the process resolves, leaving the original slight scar. The characteristic of the reaction, whatever the source of infection, is the tremendous exudative or serous response, with very little cellular and proliferative or fibroid change.

DIFFERENTIAL DIAGNOSIS

The acute benign form of tuberculosis must be differentiated from the other acute forms of pulmonary tuberculous infection. Chief among these is acute caseous pneumonia. In this latter type of disease there is a tremendous exudation which goes on to a coagulation necrosis. There is massive caseation. As this is sloughed out and expectorated, there is true cavity and antrum formation. Following this there may be a considerable cellular reaction, with the result that fibroid changes occur with the production of scar-tissue about the disease area.

How different from the benign form! Both start with a sudden onset. In their typical examples, the patient with a benign exudative lesion is not very sick or toxic and after a few days or a week feels perfectly well. The man with the caseous pneumonic type, on the other hand, is sick and toxic and remains so for a considerable time. His cough is severe and persistent and is productive of a profuse expectoration which is laden with tubercle bacilli. This is in marked contrast to the benign form in which the cough is slight and transitory, the sputum scant, and the tubercle bacilli very hard to find. The physical findings too are generally quite different. The benign form gives rise to slight dulness, diminished breathing and occasional fine moist râles. The caseating form on the other hand usually produces loud altered breathing and many medium and coarse moist râles. The single X-ray is not of much help in differentiating the two forms, especially if the benign form is X-rayed during its stage of irregular resolution. It will then appear very much like the caseous pneumonic type with excavation. Occasionally it is very difficult to differentiate the benign and the malignant form of acute tuberculosis. This is true not only on X-ray but also physical examination. When such is the case there is but one thing to do, namely, to keep the patient on absolute bed-rest and to watch him closely. The benign form will clear up. The caseous pneumonic form tends to excavate, or at any rate does not clear as rapidly. Table 1 summarizes the differential diagnosis between the acute benign and the acute malignant forms of pulmonary tuberculosis.

This suggests to us the method of treatment. These patients should be put to bed and kept in bed until all trace of their lesion has disappeared. This usually means a period of six weeks to three months. Following this, if the reaction has been due to an exogenous dose, it is our opinion that these patients may resume their former occupation without any further curing. One thing, however, is important. These patients must be protected against contact with further infection. Usually some member of the household is the offending party. Therefore all contacts must

TABLE 1

	ACUTE BENIGN (EXUDATIVE)	ACUTE MALIGNANT (CASEOUS PNEUMONIC)
Symptomatology		
Onset	Acute	Acute
Cough	Slight or absent	Moderately severe; always present
Expectoration	Scant or absent	Copious
Haemoptysis	At onset	May occur at any time
Temperature	Elevated only at onset	Irregular; elevated for a considerable time
Pulse	Elevated only at onset	Irregular; elevated for a considerable time
Physical findings		
Breath-sounds	Diminished in intensity; slight alteration in quality	Harsh with gross changes from the normal quality
Râles	Few and variable; never coarse; usually disappear early	Many and coarse; persistent
Percussion note	Dull	Dull to flat
Laboratory findings		
X-ray	Resolves often without leaving a trace	Progresses to antrum formation; fibrosis with pleural and mediastinal changes
Bacilli	Present only at onset, then absent	Many present
Course	Brief duration	Prolonged activity

be thoroughly examined for the possibility of an open case of tuberculosis. Another very interesting problem is also raised. If these patients are hypersensitive to tubercle bacilli, and we believe they are, then placing them in a tuberculosis sanatorium, as is now the general practice, will only subject them to further dosage with corresponding recurrences. This we have found to be the course of events quite frequently. We believe that this type of case should be isolated from contact with tubercle

TABLE 2

CASE NUMBER	AGE	ONSET	INITIAL EXAMINATION						
			Cough	Expectoration		Haemoptysis	Toxaemia	Physical findings	Ext
				Sputum	Tubercle bacilli				
1	22	acute	yes	yes		yes	severe	dulness, dim. br. & fine râles left chest	mod. a
2	14	acute	yes	yes	negative	no	moderate	bronchoves. br. & moist râles	mod. a
3	19	gradual	yes	yes	negative	yes	slight	few fine râles rt. upper lobe	far ad
4	27	acute	yes	yes	positive	yes	moderate	scant; few fine râles left & rt.	far ad
5	21	acute	yes	yes	negative	no	severe	dulness, br.-v. br. & fine râles over rt. upper lobe	mod. a
6	26	acute	yes	yes	negative	no	moderate	dulness, br.-v. br. apex to 5 vert. spine on right	mod. a
7	19	acute	yes	yes	negative	no	slight	fine râles root to rt. up. lobe	min.
8	18	acute	yes	yes	positive	yes	slight	br.-v. br. & fine râles left root	far adv
9		acute	yes	yes	positive	yes	severe	few fine râles left root ant.	min.
10	30	gradual	yes	yes		no	slight	br.-v. br., fine râles lt. up.	mod. a
11	25	acute	yes	yes		no	moderate	br.-v. br., fine râles rt. up.	far adv
12	28	acute	yes	yes		yes	moderate	br.-v. br., med. râles left up.	far adv
13	28	acute	no	no		no	moderate	left pleural effusion, br.-v. br. & râles apex left up.	far adv
14	22	acute	yes	yes		yes	slight	dulness, br.-v. br., fine râles apex left up.	far adv
15	20	acute	yes	yes	positive	no	severe	coarse râles lower half left ant.	far adv
16	46	acute	yes	yes		no	moderate	br.-v. br., fine râles rt. interscap.	min.
17	16	acute	yes	yes		no	severe	med. râles left up.	far adv
18	26	acute	yes	yes		yes	severe	br.-v. br. over left up.	far adv
19	25	see remarks				no	slight		far adv
20	13	acute	yes	yes	positive	yes	severe	dulness, br.-v. br., many fine râles upper ½ rt. lung; br.-v. br. fine râles over left up.	far adv
21	18	acute	yes	yes		no	slight	fine râles rt. up.	min.
22	18	acute	yes	yes	positive	yes	moderate	scant	far adv
23	29	acute	yes	yes	positive	no	severe	dulness, fine râles left up.	far adv
24	32	acute	yes	yes	positive	no	none	pleural effusion plus fine râles left up.	far adv
25	21	acute	yes	yes	positive	yes	slight	dulness, br.-v. br., few fine râles over rt. up. lobe	far. adv
26	20	acute	yes	yes	positive	yes	slight	dim. br.-v. br., many fine râles to 5 rib on left	far adv
27	33	gradual	yes	no		no	slight	br.-v. br., few fine râles rt. interscap.	far adv
28	16	acute	yes	yes	positive	no	severe	br.-v. br., fine râles ⅔ lt. lung	far adv
29	22	acute	yes	yes	positive	no	slight	br.-v. br., fine râles rt. base	mod. a
30	24	acute	yes	yes	positive	yes	slight	few fine râles at rt. root area	minima
31	67	acute	yes	yes	positive	no	severe	dim. br., fine râles left up.	far adv
32	23	acute	yes	yes	negative	yes	moderate	normal	mod. a
33	16	acute	yes	yes	positive	yes	moderate	dulness, br.-v. br., few fine râles rt. up.	far adv
34	18	acute	yes	yes	negative	yes	severe	dulness, dim. br.-v. br., fine râles left interscap.	far adv
35	18	acute	yes	yes		no	moderate	signs of fluid at base	min. effus
36	27	acute	yes	yes	positive	no	moderate	br.-v. br. & med. râles left up.	far adv
37	32	acute	yes	yes	positive	yes	moderate	br.-v. br. & med. râles rt. up.	far adv

TABLE 2

	X-RAY		CONTACT	COURSE				REMARKS
	Extent	Annular shadow		Symptoms	Physical findings	X-ray	Weight gain	
nest	mod. adv.		yes	gradual disappearance	scant	rapid clearing	12	
	mod. adv.		no (enlarged nodes)	rapid improvement	gradual lessening	clearing	15	transferred to Sea View
	far adv.	yes	neg.	rapid improvement	rapid disappearance of abnormalities	rapid clearing	7	annular shadow, disappearing in 28 days
	far adv.	yes	no	rapid improvement	normal	clearing	7	given antisyphilitic treatment (arsenic), no ill effects
rt.	mod. adv.	no	neg. sinus in neck		rapid clearing	rapid clearing	26	
ine	mod. adv.	no	no	rapid improvement	rapid clearing	rapid clearing	20	
	min.	no	no	rapid disappearance	scant	rapid clearing		
	far adv.	yes	no	rapid disappearance	scant	rapid clearing	8	
	min.	no	?	rapid disappearance	normal	rapid clearing	14	has recently had another acute process
	mod. adv.	yes	no	rapid disappearance	sib. râles lt. up.	rapid clearing	2½	
	far adv.	yes	no	rapid disappearance	normal	rapid clearing	40	
	far adv.	yes	no	rapid disappearance	normal	rapid clearing	20	complete clearing in 5 months
les	far adv.	yes	no	rapid disappearance	normal	rapid clearing	20	
eft	far adv.	yes	no	rapid disappearance	normal	rapid clearing	14½	complete disappearance in 6 mos.
	far adv.	yes	no	rapid disappearance	normal	rapid clearing	12	complete disappearance after bed-rest
	min.	no	yes	rapid disappearance	normal	none taken		patient improved so much that 2nd exam. refused
	far adv.	yes	no	rapid disappearance	normal	rapid clearing	8	
	far adv.	yes	no	rapid disappearance	normal	rapid clearing	40	
	far adv.	yes	no	rapid disappearance	normal	rapid clearing	20	disappearance of shadow in 2 mos. Seen after return from sanatorium
les les	far adv.	yes	yes	rapid improvement	rapid clearing, few fine râles both apices	rapid clearing	30	original cavity and inflammatory reaction quickly disappeared; original prognosis hopeless
	min.	no	no	rapid disappearance	normal	rapid clearing	12	improved in 6 wks.
	far adv.	yes	no	rapid disappearance	normal	rapid clearing	20	
	far adv.	yes	no	rapid disappearance	normal	rapid clearing	31	
p.	far adv.	yes	no	rapid disappearance	normal	rapid clearing	11	
ver	far. adv.	yes	no	rapid disappearance	normal	rapid clearing	14	
rib	far adv.	yes	no	rapid improvement	clearing	rapid clearing	15	still under treatment
.	far adv.	yes	yes	rapid disappearance	normal	rapid clearing	3	still under treatment
	far adv.	yes	?	rapid disappearance	clearing	rapid clearing	6	still under traetment
	mod. adv.	no		rapid disappearance	normal	rapid clearing	8	still under treatment
	minimal	no	no	rapid disappearance	normal	rapid clearing	24	still under treatment
	far adv.	yes	no	rapid disappearance	normal	rapid clearing		still under treatment
	mod. adv.	no	?	rapid disappearance	normal	rapid clearing		
up.	far adv.	yes	no	rapid disappearance	normal	rapid clearing	10	
eft	far adv.	yes	no	rapid disappearance	normal	rapid clearing		
	min. plus effusion	no	yes	no symptoms	clearing	rapid clearing		still under treatment
	far adv.	yes	yes	rapid disappearance	normal	rapid clearing	43	
	far adv.	yes	no	placed in Veterans' Hospital Bureau. Letter after one month stated gain 5 lbs. and disappear-				

								upper ⅓ rt. lung; br.-v. br. fine râles over left up.	
21	18	acute	yes	yes		no	slight	fine râles rt. up.	min.
22	18	acute	yes	yes	positive	yes	moderate	scant	far adv.
23	29	acute	yes	yes	positive	no	severe	dulness, fine râles left up.	far adv.
24	32	acute	yes	yes	positive	no	none	pleural effusion plus fine râles left up.	far adv.
25	21	acute	yes	yes	positive	yes	slight	dulness, br.-v. br., few fine râles over rt. up. lobe	far. adv
26	20	acute	yes	yes	positive	yes	slight	dim. br.-v. br., many fine râles to 5 rib on left	far adv.
27	33	gradual	yes	no		no	slight	br.-v. br., few fine râles rt. interscap.	far adv.
28	16	acute	yes	yes	positive	no	severe	br.-v. br., fine râles ⅔ lt. lung	far adv.
29	22	acute	yes	yes	positive	no	slight	br.-v. br., fine râles rt. base	mod. ad
30	24	acute	yes	yes	positive	yes	slight	few fine râles at rt. root area	minimal
31	67	acute	yes	yes	positive	no	severe	dim. br., fine râles left up.	far adv.
32	23	acute	yes	yes	negative	yes	moderate	normal	mod. ad
33	16	acute	yes	yes	positive	yes	moderate	dulness, br.-v. br., few fine râles rt. up.	far adv.
34	18	acute	yes	yes	negative	yes	severe	dulness, dim. br.-v. br., fine râles left interscap.	far adv.
35	18	acute	yes	yes		no	moderate	signs of fluid at base	min. effusi
36	27	acute	yes	yes	positive	no	moderate	br.-v. br. & med. râles left up.	far adv.
37	32	acute	yes	yes	positive	yes	moderate	br.-v. br. & med. râles rt. up.	far adv.
38	24	acute	yes	yes	positive	no	severe	coarse râles both interscap.	far adv.
39	33	acute	no	yes	negative	yes	none	not seen at onset	far adv.
40	23	acute	yes	yes	positive	no	moderate	normal	far adv.
41	22	acute	yes	yes	positive	no	slight	br.-v. br. & med. râles left up.	far adv.
42	45	acute	yes	yes	positive	no	moderate	dulness br.-v. br., med râles over rt. up.	mod. ad
43	21	acute	yes	yes	positive	no	moderate	v. br. & med râles left up.	far adv.
44	59	acute	yes	yes		yes	severe	dulness, few fine râles, rt. root	far adv.
45	17	acute	yes	yes	negative	yes	slight	br.-v. br., many med. râles rt. up.	min.
46	19	acute	yes	yes	positive	yes	moderate	med. râles lower rt. interscap.	far adv.
47	17	acute	yes	yes	negative	no	moderate	dulness, br.-v. br. lt. apex	far adv.
48	35	acute	yes	yes	negative	yes	severe	med. râles rt. lower	mod.
49	20	no symptoms	no sputum					râles rt. lower & rt. middle	mod.
50	21	acute	yes	no		yes	moderate	br.-v. br., râles rt. up.	far adv.
51	9	acute	yes	no		no	slight	med. râles rt. up.	mod. ad
52	57	gradual	yes	yes		no	slight	varied with location of lesion, br.-v. br. râles	far adv.
53	34	acute	yes	yes		no	slight	br.-v. br. & few fine râles rt. lower	min.
54	22	acute	yes	yes		no	slight	few fine râles rt. root	min.
55	23	see case report	yes					normal	
56	52	acute	yes	yes	negative	no	moderate	br.-v. br., râles left up.	mod. ad
57	23	acute	yes	yes	positive	yes	none	br.-v. br. & râles left base	far adv.
58	25	acute	yes	yes	positive	yes	moderate	coarse râles rt. lower	far adv.

					few fine râles both apices			inflatory reaction quickly disappeared; original prognosis hopeless
	min.	no	no	rapid disappearance	normal	rapid clearing	12	improved in 6 wks.
	far adv.	yes	no	rapid disappearance	normal	rapid clearing	20	
	far adv.	yes	no	rapid disappearance	normal	rapid clearing	31	
o.	far adv.	yes	no	rapid disappearance	normal	rapid clearing	11	
er	far. adv.	yes	no	rapid disappearance	normal	rapid clearing	14	
ib	far adv.	yes	no	rapid improvement	clearing	rapid clearing	15	still under treatment
	far adv.	yes	yes	rapid disappearance	normal	rapid clearing	3	still under treatment
	far adv.	yes	?	rapid disappearance	clearing	rapid clearing	6	still under traetment
	mod. adv.	no		rapid disappearance	normal	rapid clearing	8	still under treatment
	minimal	no	no	rapid disappearance	normal	rapid clearing	24	still under treatment
	far adv.	yes	no	rapid disappearance	normal	rapid clearing		still under treatment
	mod. adv.	no	?	rapid disappearance	normal	rapid clearing		
p.	far adv.	yes	no	rapid disappearance	normal	rapid clearing	10	
ft	far adv.	yes	no	rapid disappearance	normal	rapid clearing		
	min. plus effusion	no	yes	no symptoms	clearing	rapid clearing		still under treatment
	far adv.	yes	yes	rapid disappearance	normal	rapid clearing	43	
	far adv.	yes	no	placed in Veterans' Hospital Bureau. Letter after one month stated gain 5 lbs. and disappearance of symptoms. X-ray clear after 2 years (when next seen by us).				
	far adv.	yes	?	rapid disappearance	normal	rapid clearing	20	
	far adv.	no	no	rapid disappearance	normal	rapid clearing	23	
	far adv.	yes	no	rapid disappearance	normal	rapid clearing	48	
	far adv.	yes	yes	rapid disappearance	few râles left apex; see case report		43	
p.	mod. adv.	no	yes	rapid disappearance	normal	rapid disappearance	5	
	far adv.	yes	yes	rapid disappearance	normal	rapid disappearance	15	
	far adv.	yes	no	rapid disappearance	normal	rapid disappearance	3	diabetic
	min.	no	yes	rapid disappearance	normal	rapid disappearance	6	
	far adv.	yes	yes	rapid disappearance	normal	rapid disappearance		
	far adv.	yes	no	rapid disappearance	normal	rapid disappearance	36	
	mod.	no	(apical lesion)	rapid disappearance	normal	rapid disappearance	18	history of apical tuberculosis 18 yrs. previously
	mod.	no	(mediastinal abscess)	no symptoms				see case report
	far adv.	yes	?	rapid disappearance	normal	rapid disappearance		see case report
	mod. adv.	no	no	rapid disappearance	normal	rapid disappearance	15	
v.	far adv.	no	no	rapid improvement	varied with changes in lesion	complete disappearance with reappearance in new areas	15	still under treatment
	min.	no	yes	rapid disappearance	normal	rapid clearing	4	
	min.	yes	no	rapid disappearance	normal	rapid clearing see case report	12	
	mod. adv.	no	no	rapid disappearance	rapid clearing	complete disappearance 5 mos.	22	
	far adv.	yes	no	rapid disappearance	normal clearing	rapid clearing	10	
	far adv.	yes	yes	rapid disappearance	rapid clearing	rapid clearing	30	

bacilli, either by being treated away from the tuberculosis centre or else in a sanatorium where special effort is made to prevent cross-infection, either by means of the cubicle system and strict isolation or by some similar procedure.

Our work has been based on a study of 58 cases. These case reports have been summarized in table 2.

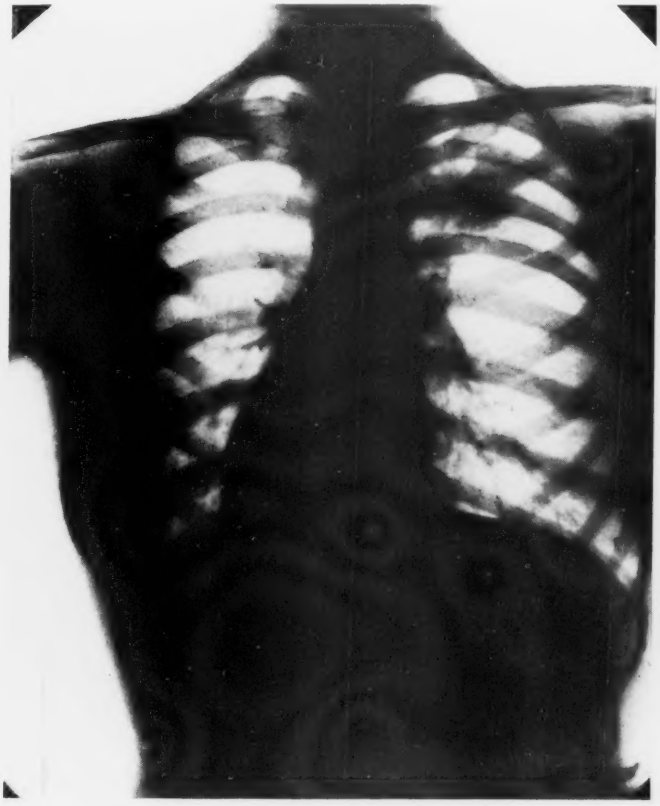

FIG. 1

The reporting of 58 cases in detail would be monotonous, the course being typical and unvarying. The following are selected from the above group:

Case 2257: A young lady, seventeen years of age, white, states she has been ill for one week. Her illness began with an acute cold in the head accompanied

by cough and expectoration. The expectoration was scant and occasionally it was blood-streaked. With the beginning of her cold she had some elevation of temperature which quickly subsided. Her past history was irrelevant except for the fact that there was a history of contact with an open case of far-advanced tuberculosis. Her fiance was sent to Saranac Lake and, previous to her illness, she had been to Saranac Lake to visit him for one month.

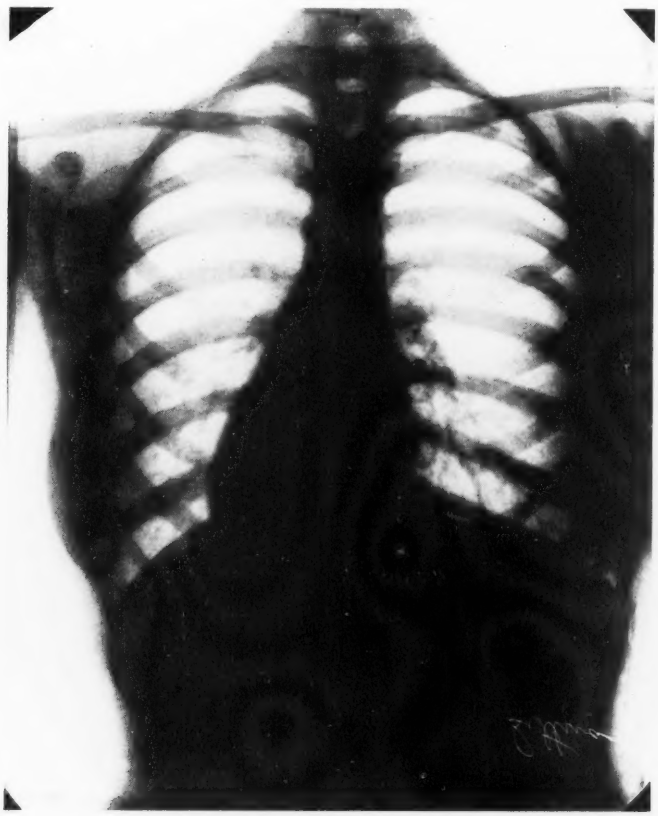

FIG. 2

Physical Examination: The examination revealed evidence of a pathological process in the right upper lobe. There were altered breath-sounds (broncho-vesicular) and moist râles in the right upper lobe from the apex to the third rib anteriorly and to the fourth vertebral spine posteriorly.

X-Ray Examination: The examination demonstrated a parenchymatous infiltration, minimal in amount and exudative in character.

Course of Disease: The patient was put on complete rest in bed. In a few

days her symptoms disappeared. She had no cough or expectoration. The sputum examination revealed no acid-fast bacilli. Forty-nine days later she was again X-rayed. The pathological changes noted previously had completely disappeared, leaving no trace of their existence. Physical examination revealed a normal right lung. The patient had made an uneventful recovery in forty-nine days and has been in good health since then.

Case 2382: A young lady, white, nineteen years of age, caught cold one month ago. She began to cough and expectorate but continued going to her work. She was fatigued and felt warm but did not take her temperature. Two weeks after her illness she was forced to take to bed. Her cough had become worse and she developed a huskiness in her voice. While in bed she expectorated some blood, less than a teaspoonful, and her sputum remained blood-streaked for a week. Her temperature when she went to bed was 101, and in a few days subsided to normal. In spite of the blood-streaked sputum her cough and expectoration began to subside after rest in bed. Her past history was irrelevant except for a history of contact with an open case of tuberculosis. Her sister-in-law had lived at her home for about six months and had recently left for the country. Her local physician had diagnosed her condition as an unresolved pneumonia. With the experience of her sister-in-law, she came to the office of one of us for a check-up.

Physical Examination: The examination revealed the following: *Right Lung:* There was some dulness over the lower half of the lung, and bronchovesicular breathing over the apex of the upper lobes; no râles. Over the lower and middle lobes some altered breathing and moist râles were heard. *Left Lung:* There was no modification of breath-sounds nor râles.

X-Ray Examination: The examination demonstrated a basal lesion in the lower half of the right lung. Close to the root area there was an annular shadow which extended approximately from the midline of the third interspace to the lower margin of the fifth rib anteriorly. The process resembles an acute caseous pneumonic form of tuberculosis. Figure 3 is the X-ray described above.

Sputum Examination: Tubercle bacilli were demonstrable.

Course of Disease: The patient was put to bed on complete rest. Her cough and expectoration rapidly disappeared. Her physical findings began to disappear but not as rapidly as her symptoms. The X-ray shadows showed rapid clearing. Figure 4 shows the X-ray taken forty-three days later. The annular shadow has disappeared. In figure 5, the X-ray is forty-three days later and more parenchymal clearing is noted. By this time all symptoms and signs have disappeared. There were a few inconstant râles over the right lower lobe. The next X-ray (figure 6) was taken after a summer vacation and demonstrates the complete resorption of the pathological changes shown by

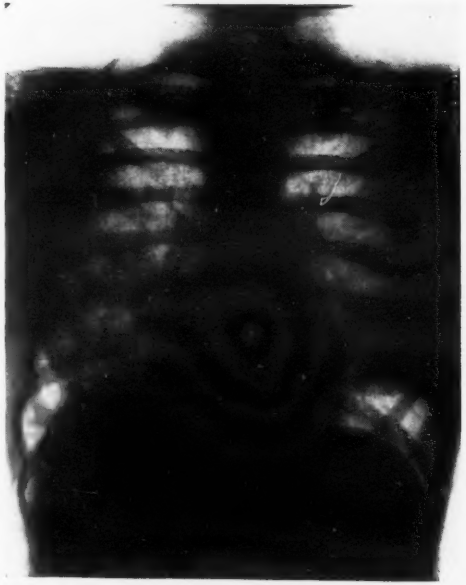

FIG. 3

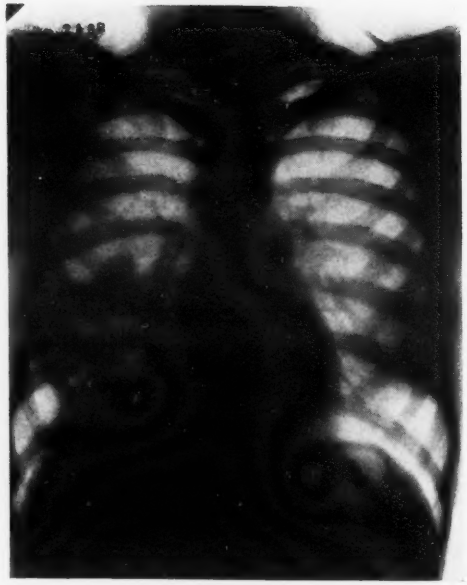

FIG. 4

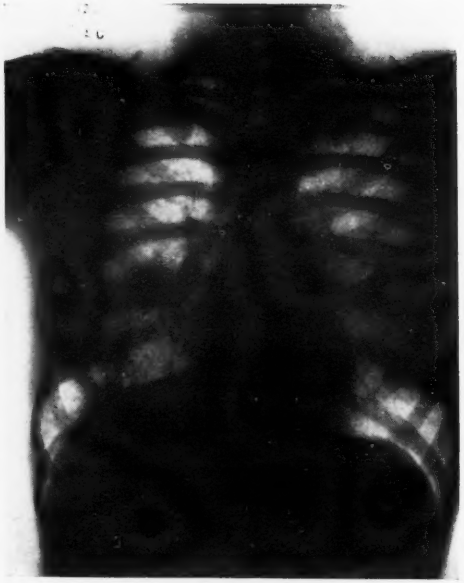

FIG. 5

Fig. 6

Fig. 7

Fig. 8

X-ray. In figures 7 and 8 one would question whether tuberculous disease had ever existed in the right lung. The course of the disease has been uneventful and the patient is now at work and enjoying good health.

Case 1261: A male, white, student, twenty-three years of age, complained of being ill for one month. His illness began with a chill. He immediately began to cough and expectorate. He felt very weak and easily became exhausted. He expectorated no blood. After a few days in bed he returned to school. In the past four weeks he lost four pounds. He came for an examination chiefly because of the marked fatigue he experienced. His previous history was irrelevant. There was no history of a tuberculous contact.

Physical Examination: The examination revealed scant findings in the right upper lobe. There were dulness and altered breath-sounds. No râles were heard.

X-Ray Examination: The examination demonstrated a moderately advanced tuberculosis in the right upper lobe (figure 9). The process was close to the axilla and extended from the first rib down to the fifth rib anteriorly. Close to the axilla there was an annular shadow which extended down from the lower margin of the second rib to the lower margin of the third rib anteriorly. It occupied the outer fourth of the second interspace. The process resembled a caseous pneumonia which had sloughed out, leaving a fair-sized antrum.

Sputum Examination: Acid-fast bacilli were demonstrated in the sputum.

Course of Disease: The patient lived in the country and it was decided to put him to bed for a few weeks. His symptoms rapidly disappeared. Examination in a month revealed no physical findings. The patient was kept in bed for three months. Because of the long journey to the office he was not X-rayed until eight months later. The X-ray (figure 10) demonstrated a complete disappearance of his pathological process. An X-ray taken one year later (figure 11) demonstrated no evidence of tuberculous changes. The patient enjoyed good health since January, 1926.

Case 3465: A colored male, age thirty-two, ten days before being seen, suddenly had a chill, fever, pain in the right lower chest and a productive cough. These subsided so that, when first examined, a slight morning cough was the only remaining symptom. There was no history of any previous illness except occasional head and chest colds. There was no history of contact with tuberculosis.

Physical Examination: Examination revealed a well-developed and nourished negro who did not appear ill. His temperature was 98.2°, pulse 84, respirations 20, and weight 115; his normal weight was 130. Physical signs in the lungs consisted of diminished resonance, many fine high-pitched moist râles, and an area of bronchial breathing on the right at the level of the third

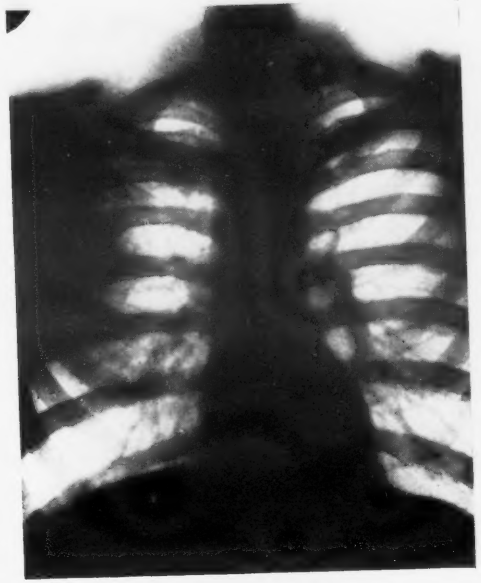

FIG. 9

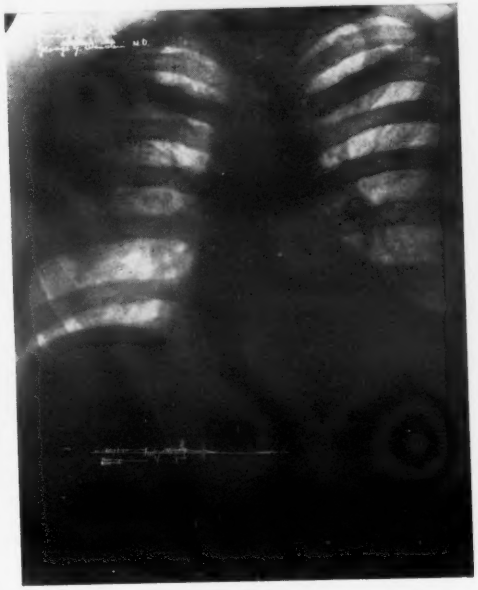

FIG. 10

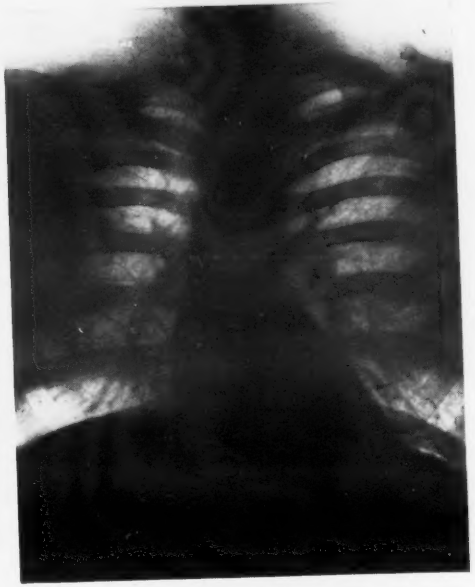

FIG. 11

rib. At the left base, below the angle of the scapula, breath-sounds were harsh, with a few fine moist râles.

X-Ray Examination: X-ray taken at this time (figure 12) showed an area of diffuse haziness, with irregular densities extending out from the root toward the lower pulmonary zone. The upper margin was sharply delimited by the interlobar fissure between the upper and middle lobes.

Course of Disease: In spite of repeated urgings to rest, this patient continued to work. One month later there was merely harsh breathing with slight dulness on the right. The râles had disappeared. X-ray showed a marked clearing. By this time the patient felt perfectly well and could be prevailed upon to return for examination only with the greatest difficulty. Three months after admission, signs on the right had cleared completely. At the left base there were bronchovesicular breathing and moist râles. X-ray showed progressive but not complete clearing on the right. No lesion was to be seen in any other part. At this time it was found that the patient had a four-plus Wassermann. Active antisyphilitic treatment was accordingly instituted. The patient gained three pounds.

Six months after the first examination the patient returned for reëxamination with the story of a chest cold and productive cough for the past few days. He had lost the previous gain of three pounds. Examination of the chest showed a normal right lung. On the left there was harsh breathing over the lower lobe with a coarse friction rub over the base in the axillary line. Figure 13 shows the X-ray appearance at this time. There was a clearing of the shadow on the right except for a thickening of the interlobar pleura. On the left side, however, irregular dense shadowing was present below the level of the fourth rib. Since his previous visit the patient had received four intravenous injections for his syphilis. On this visit, for the first time, he stated that his mother-in-law, with whom he had been living, has "heart disease with a cough." Further investigation of this member of the family revealed extensive tuberculosis. The source of infection was then removed. Ten weeks later all evidence of the pulmonary process had disappeared, both on physical examination and on X-ray examinations. Figure 14 shows the X-ray appearance at this time. The patient had gained four pounds. The sputum throughout the disease was negative. However, the patient was rather uncoöperative, which might have helped to account for this fact. This case illustrates well the recovery following removal of contact.

Case 2974: A female, housewife, aged forty-four, has been ill for six weeks. Her illness began with cough and expectoration, night-sweats and weakness. Her expectoration was copious at first but has diminished. She complained of pain over the left thorax and sternum. There was no haemoptysis. The past history is irrelevant. The patient's brother, who has been living with her, has

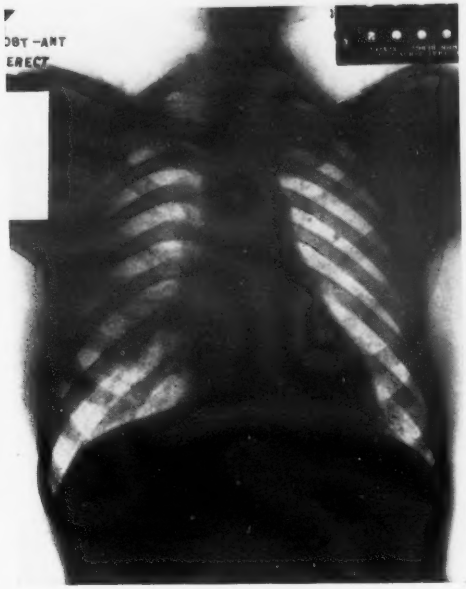

FIG. 12

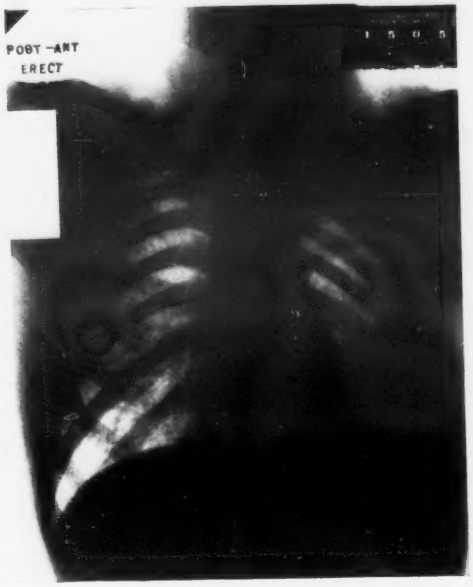

FIG. 13

FIG. 14

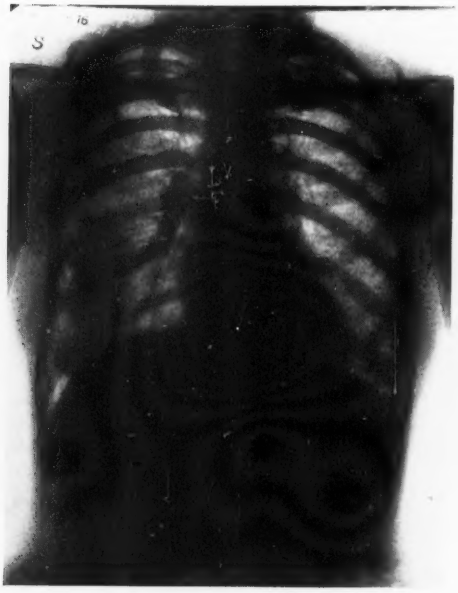

FIG. 15

FIG. 16

an open case of tuberculosis. She was diagnosed by her local physician as a case of bronchopneumonia. Because of her fatigue and rapid loss of weight she came to the office of one of us for an opinion.

Physical Examination: The examination revealed that the right lung was involved. At the apex of the upper lobe bronchovesicular breathing with some fine moist râles was heard. Dulness was elicited over the lower lobe on percussion. Altered breathing and moderately coarse râles were heard over the whole lower lobe. The left lung was not involved.

X-Ray Examination: The examination revealed a tuberculous process (figure 15) in the right lung. It extended from the second rib to the base of the lung. In the upper lobe it was chiefly in the second interspace. There was a massive infiltration in the lower lobe that looked like a caseous pneumonic process before it had softened.

Sputum Examination: Tubercle bacilli were found in the sputum.

Course of Disease: The patient was put on complete rest in bed. In two weeks she lost her cough and expectoration. Her weight increased. The physical findings had disappeared. An X-ray taken fourteen days later (figure 16) showed a clearing of the process. The progress of the patient was so rapid that she refused to come for any further check-up. Her local physician informs us that the patient is enjoying the best of health and is carrying on all her household duties.

Case 2829: A young lady, white, seventeen years of age, complains of being ill for the past month. Illness began with a cold in the head, the infection passing down into her bronchial tubes. After a few days she had a temperature of 102°, which persisted for a few days and subsided slowly, reaching normal in the morning with a slight afternoon rise. The first month the cough was nonproductive. For one week it was productive and then was again dry. She fatigues easily, sweats at night and has been hoarse. She expectorated no blood. She lost eleven pounds in weight.

Physical Examination: The examination of the lungs revealed physical findings in the left upper lobe. There was dulness over the left upper lobe both anteriorly and posteriorly. Altered breath-sounds and râles were heard anteriorly over the left upper lobe from the apex to the second rib. The râles were moderately coarse and moist and were more numerous close to the sternum. The weight was ninety-seven pounds.

X-Ray Examination: An X-ray taken on November 9, 1928 (figure 17) demonstrates a tuberculous infiltration in the left upper lobe extending from the apex to the third rib anteriorly. There is a large annular shadow occupying the outer third of the first interspace. The appearance of the film is that of a caseous pneumonic tuberculosis with a large cavity in the upper lobe.

Course of Disease: The patient raised no sputum and therefore it was not

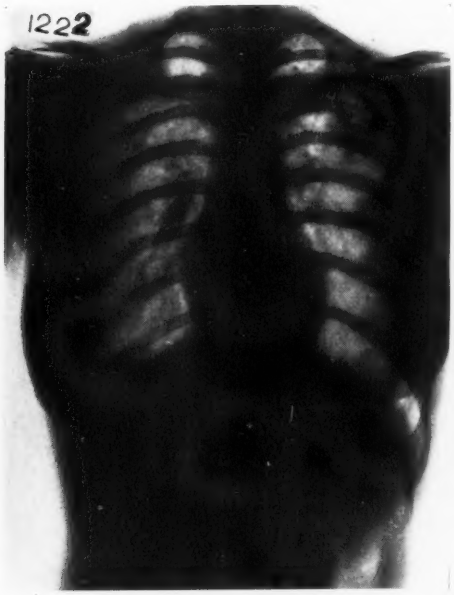

FIG. 17

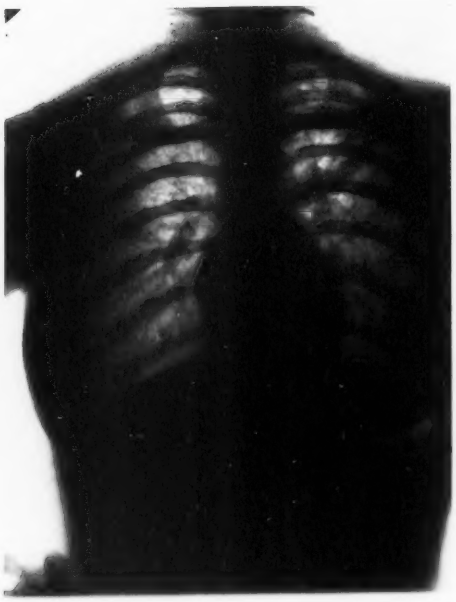

FIG. 18

possible to examine for acid-fast bacilli. She was put on complete rest in bed. Her symptoms and physical findings disappeared in two weeks. Her next X-ray (figure 18), taken forty days later, demonstrates a complete disappearance of the annular shadow and considerable resorption of the tuberculous changes. She gained eighteen pounds in weight in forty days. She has made an uneventful recovery with almost complete disappearance of her lesion.

Case 2780: Male, Porto-Rican, was admitted to the hospital September 7, 1929. His present illness began five months ago, when he developed a few

FIG. 19

abscesses on the anterior portion of his chest. His family physician incised them. They did not heal but kept on discharging. He coughed slightly but did not expectorate. He complained of pain over his thorax. He went to Mt. Sinai Hospital where a diagnosis of far-advanced pulmonary tuberculosis was made. He was then transferred to the Metropolitan Hospital.

Physical Examination: The examination of the lungs revealed no evidence of disease. There was a small discharging sinus to the right of the sternum about opposite the third rib.

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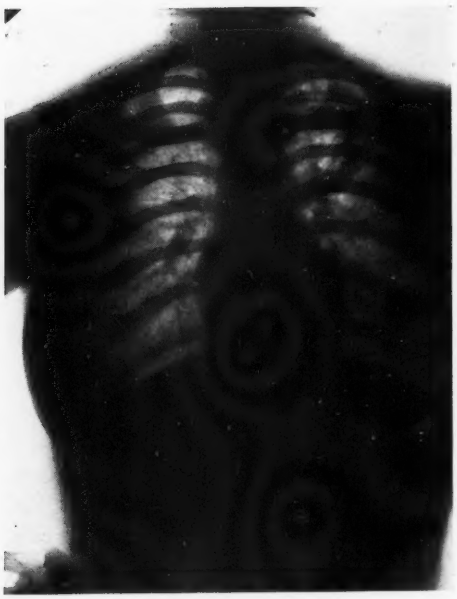
FIG. 17



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Physical Examination: The examination of the lungs revealed no evidence of disease. There was a small discharging sinus to the right of the sternum about opposite the third rib.

X-Ray Examination: An X-ray taken on September 10, 1929 (figure 19) demonstrated no evidence of pulmonary tuberculosis. The report from Mt.

Sinai Hospital described an X-ray taken on August 6, 1929, as a far-advanced tuberculosis involving the left lung. Figure 20 is a copy of that X-ray. In about a month there was a complete disappearance of the lung involvement.

Course of Disease: A few weeks later the sinus was injected with lipiodol (figure 21), which was found to cross over to the left axilla from the right thorax. Apparently it was a cold abscess that had burrowed its way anterior to the parietal pleurae from the vertebral spine, going around the left thorax to open to the right of the sternum. It probably opened into the lung, causing

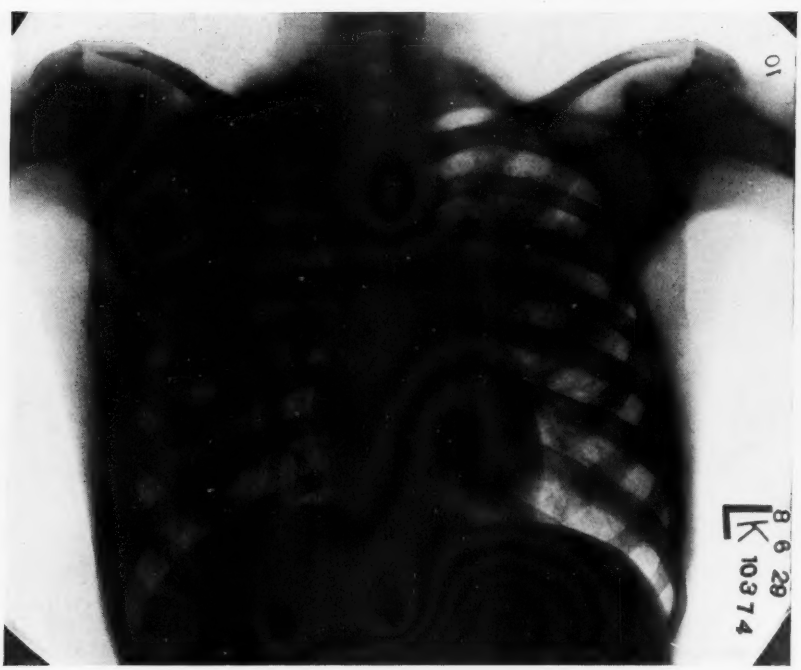

FIG. 20

this extensive pulmonary involvement, the reaction being similar to a Koch phenomenon. The rapid resorption can be seen in the X-ray (figure 19).

Subsequently the patient developed another sinus over the upper part of the sternum. He then developed a caseous pneumonic process in the left lung and had a down-hill course. His sputum then became constantly positive. The reinfections came endogenously from the cold-abscess tracts around the thorax.

Discussion: This is an interesting case and demonstrates how easily one can misjudge the ability of other workers. Had we not been familiar with this type of tuberculosis we would have believed the diagnosis was erroneous.

Having seen so many of these cases we immediatey made a diagnosis of acute benign pulmonary tuberculosis and sent for a copy of the original X-ray for our files. Had there been no reinfection the patient would have had a good prognosis.

FIG. 21

SUMMARY

We have described an acute form of tuberculosis. Its onset is sudden, its course brief, and its resolution complete. The symptoms are slight, —slight cough and expectoration for a few days and then their disappearance. Blood-spitting is apt to be the initial symptom; it so occurred in 43 per cent of our cases. After the first week the patient usually feels perfectly well. The physical signs are scant, dulness and diminished breathing being the most usual findings. X-ray shows a dense shadow of varying extent, usually classified as far-advanced. In fact, 62 per cent of our cases fell into this group according to the standards of the National Tuberculosis Association. Only 20 per cent were moderately advanced while 18 per cent had a minimal lesion. This shadow may resolve in a few weeks to a few months, leaving a clear lung field. This shadow in its disappearance may be absorbed uniformly or else irregularly,

producing an appearance suggestive of cavitation. The benign form of tuberculosis which we have described has been frequently confused with the acute malignant form which goes on rapidly to caseation. A scheme of differential diagnosis has been presented. The treatment is rest in bed till all X-ray evidence of the lesion has disappeared. In 22 per cent of our cases there was a definite history of exposure to tuberculosis. The patient must be protected from further contact with tubercle bacilli.

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A CLINICAL CLASSIFICATION OF PULMONARY TUBERCULOSIS[1]

GEORGE G. ORNSTEIN, DAVID ULMAR AND EDGAR LEON DITTLER

All who have had any experience with cases of pulmonary tuberculosis have no doubt been astounded at times by the remarkable differences in the clinical course of cases which seemingly were identical in type when first seen. Both of two cases may have been far-advanced cases according to the present classification of tuberculosis as standardized by the National Tuberculosis Association. Yet one of them completely clears up within the short space of two to three months while the other persists to the end of the patient's life. At other times a so called cavity, as judged by X-ray appearances, which automatically places the case in the far-advanced group, disappears within a few weeks. It is not our conception of pathology that cavities can act in this manner. It seems to us that in order to justify its existence a classification must accomplish some purpose and must be based on a sound and logical system of measurement. This classification should take into consideration not only the various types of pathological process, which in tuberculous disease assume major importance because of the tremendous difference in prognosis of the various types, but also the extent of the disease, and an approximation of the symptom-picture. Our present classification takes absolutely no cognizance of the different types of tuberculous pathological change. It seems based almost entirely on extent of disease as determined by physical signs and X-ray interpretation. To our minds it seems a failure. We are therefore proposing a modification of the National Tuberculosis Association classification of tuberculosis by the addition of a clinicopathological classification and some slight changes in the criteria to determine extent. We believe that by these changes the classification of tuberculosis can be made more rational and understandable.

A review of the literature reveals that there have been many previous attempts at an adequate workable classification. The following authors have contributed various ideas to this problem: Bard (1) (28), Ros-

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thorn and Fränkel (2), Albrecht (3), Brown (4), Buttner (5), Rathbun (6), Bacmeister (7), Nikol (8), Schmincke (9), Burrell (10), Brown, Heise and Sampson (11), Waters and Amberson (12), Romberg (13), Fränkel and Graff (14), Pissavy (15), Rockhill, Craddock and Amberson (16), Pottenger (17), Ulrici (18), Ranke (19), Nicol (20), Beitzke (21), Lydtin (22), Turban (23), Bernard (24), Sternberg (25), Cummins (26), Reisman (27), Neumann (29) (31), Toinon (30).

A list of the above-named authors with a summary of their various efforts is given in the appendix to this paper. Most of these schemes of classification are open to serious criticism. Some are illogical in their criteria of measurement. Some are tremendously unwieldy and are grossly impractical from a clinical point of view. Others seem to be based entirely on pathological conceptions as obtained at the autopsy table. Theoretically it would seem that the pathologist's classification is ideal. Actually, however, this is not the case. The pathologist sees only the end-stage which may be quite different from what the clinician has noted. This may be due, not to any error on the clinician's part, but to extensive and rapid changes which may occur, and frequently do occur, just prior to death. Naturally the pathologist, seeing only the final picture, is apt to have an erroneous concept of the disease.

We feel that a classification should be of primary value to the clinician. The scheme which we are proposing is based on our conceptions of pathology from a clinical standpoint. We have found from our experience that they are sound and during the past year have used them as the basis of our classification of tuberculosis at the Metropolitan Hospital.

The various types of tuberculous process and their pathogenesis are very easy to comprehend provided certain basic principles of tuberculous infection and of pulmonary anatomy are kept in mind. Following the primary infection with the tubercle bacillus, which usually occurs in childhood, there is a definite alteration in the reaction of the body cells to any subsequent superinfection. It is this superinfection with which we are primarily concerned in our scheme of classification. The altered reaction of the body cells assumes two different forms, one a proliferative response, the other an allergic response which is concerned primarily with the serous or exudative reaction in a tuberculous lesion.

It is our opinion that tuberculous pulmonary pathology, on the basis of these two general types of reaction, can be divided into four main divisions or classifications. We propose for clinical use the following groups: first, "Exudative;" second, "Caseous-pneumonic;" third, "Exudative-

productive;" and fourth, "Chronic-proliferative." The particular group into which the case falls will depend upon which cellular reaction predominates,—the proliferative reaction or the allergic reaction. These four types should form the basis of our classification. The anatomical extent, such as minimal, moderately advanced, or far advanced, can be applied as at present to each of the four types, with these exceptions: first, cavity shall not automatically classify the case as far advanced; second, complications shall be listed separately and shall not influence the pulmonary classification. The symptom classification "a", "b" and "c" is to be continued as at present. In the following pages we are describing our four types of pulmonary tuberculosis.

EXUDATIVE TUBERCULOSIS

Patients are frequently seen who are extremely sensitive to the tubercle bacillus and its products. They react with an intense allergic response. If a person of this sort aspirates a small amount of tuberculous material an intense exudative reaction occurs. While the irritation of the cells has been sufficient to cause a tremendous serous response, it has not been quite intense enough to cause any permanent injury or cell destruction. While there is a tremendous serous reaction, there is no ensuing necrosis or caseation that can be demonstrated clinically. After the peak of the reaction has been reached, absorption takes place. Since there has been no tissue destruction, after the exudate has been absorbed normal lung tissue remains.

Clinically, this type of tuberculosis has not been well recognized. Its onset and course suggest an ordinary acute cold. The patient is taken acutely ill with a slight cough and expectoration. Haemoptysis is fairly frequent at the onset; within a few days to a few weeks all symptoms disappear and the patient feels perfectly well. Physical findings are very slight and consist mainly of dulness, diminished breathing and a few fine râles. The X-ray is startling and shows a shadowing more or less extensive. The shadow is quick to appear and disappears almost as quickly. During its absorption its irregular clearing may cause an appearance which is often confused with the X-ray picture of the true caseous-pneumonic type. Areas of high light are seen which are often interpreted as true cavities. Serial X-rays, however, soon reveal the tremendous difference in the two types of process. The exudative type disappears, often without leaving a trace of its former presence. Not much is definitely known regarding the histological pathology of this type of tubercu-

losis. These patients recover and do not come to the autopsy table. We believe that there is probably a congestion and oedema of the alveolar walls. There then follows an exudation of serum into the alveoli with little fibrin and very few cells. There is relatively little desquamation of the epithelium. The alveolar walls remain intact, so that, when absorption of the exudate occurs, normal lung tissue remains. The prognosis is excellent.

The following cases illustrate this type of tuberculosis:

Case 1: Female, born in United States, age twenty-two, stenographer. Immediately following parturition, and one month before admission, the patient noticed fever and chills. One week later a cough developed. This cough has persisted and the sputum has been occasionally blood-streaked. Night-sweats have been present for the past three weeks. In the past the patient has had attacks of pleurisy frequently, scarlet fever at seven, measles and erysipelas at fifteen, pneumonia at eight and twelve. Six months before admission she had some blood-tinged sputum. Her grandfather died of tuberculosis. Her husband has a chronic cough.

Examination revealed a rather pale but well-nourished young woman, not ill; temperature 97.8°, pulse 112, respiration 26. Signs in the lungs were unilateral and revealed bronchovesicular breathing to the third rib and to the sixth vertebral spine with slight dulness. There were many high-pitched moist râles heard throughout the chest.

X-ray taken at this time (figure 1) showed an increase in the parenchymal markings throughout the entire right field. This was more noticeable above the third rib, anterior, than elsewhere. At the level of the first interspace was a thin-walled annular shadow, about $1\frac{1}{4}$ in. in diameter. Because of the shadow cast on the film by the metal medal which was inadvertently left in place, another film was taken three days later (figure 2). During this brief interval there was an increase in the size of the annular shadow and a slight diminution of the amount of surrounding mottling. These two films illustrate very prettily the rapidity with which changes may occur in exudative tuberculosis. Three and a half weeks later another film, shown in figure 3, revealed still further changes. The annular shadow was now rather indistinct and showed evidence of disintegrating. The surrounding mottling was very much lessened in extent. There are still abnormal physical signs present but they have diminished considerably as compared with the original examination. This patient is still curing. Her temperature has been normal, and her cough and expectoration have practically disappeared. She has gained 9 pounds. Her sputum, when obtainable, is negative. She is being kept on bed-rest. According to our scheme she would be classified, when first seen, as follows: *Exudative Tuberculosis; Extent, Stage II; Symptomatology, Group A.*

FIG. 2. CASE 1

FIG. 1. CASE 1

Case 2: Female, born in Porto Rico, age twenty-two, laundress, contracted a cold one month before admission. Her cough has persisted since then and has been slightly productive. No other symptoms are present. The patient has always been susceptible to colds which last but a few days and then disappear. There is no history of any other illness. For the past four months, since

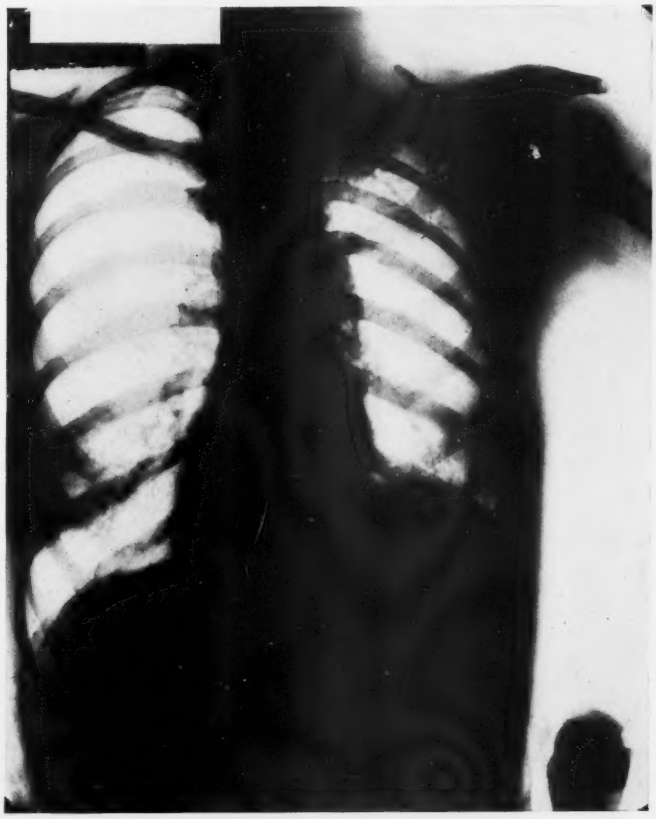

FIG. 3. CASE 1

coming to the United States from Porto Rico, the patient has been living with her two brothers, both of whom have chronic coughs.

Examination revealed a fairly well-developed and nourished young woman who did not appear ill. The temperature was 98.6°, pulse 110 and respirations 24. The physical findings in the lungs were scant. There was bronchovesicular breathing present over the right apex to the second rib. Posteriorly from the angle of the scapula to the base a moderate number of high-pitched fine moist râles were heard. X-ray taken at this time showed irregular mottled

FIG. 5. CASE 2

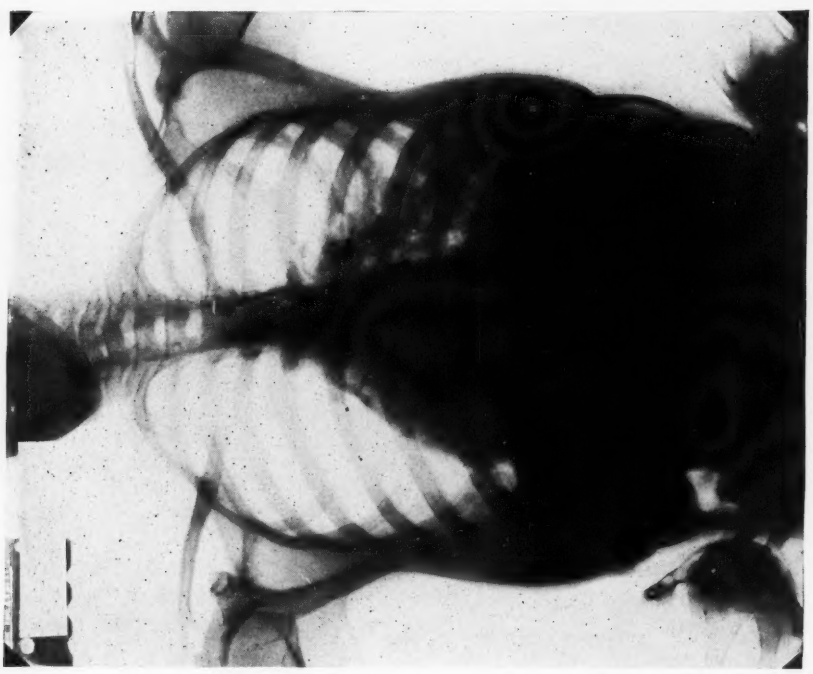

FIG. 4. CASE 2

shadowing, extending out from the right root into the lower half of the pulmonary field. A slight amount of nodular shadowing could be seen extending up as far as the second rib, anterior. The interlobar pleura between the middle and upper lobe was thickened. This film is shown in figure 4.

Following admission the patient was put on bed-rest and immediately began to improve. Her cough diminished and she began to gain weight. Her

FIG. 6. CASE 2

temperature, aside from an occasional rise to 100°, remained normal. The patient felt well and could be kept in bed only with difficulty. Nine weeks after admission examination of the chest revealed dulness and diminished breathing on the right below the level of the fourth vertebral spine. Scattered fine râles were present in the interscapular area. X-ray at this date (figure 5) showed a somewhat denser shadow over the lower lung field than was present originally. An area of high light was also noticeable at the root

area. In spite of the lack of improvement in the X-ray shadowing, and because of the excellence of the patient's general health, her absence of symptoms and paucity of physical signs, it was felt that this case was exudative in type and merited further bed-rest.

Three weeks later this patient was X-rayed again (figure 6). At this time there was marked clearing of the shadowing over the right lower field. The area of high light at the root had disappeared. Physical signs were scant, and showed merely a few scattered râles at the right base with diminished breathing. This patient is still curing. She has gained 13 pounds. Her sputum was positive on admission, and negative two weeks later. Since then she has raised no sputum. The Wassermann test was negative. She was classified when first seen as *Exudative Tuberculosis; Extent, Stage II; Symptomatology, Group B.*

Caseous-Pneumonic Tuberculosis

In this type of process, probably because of a massive dose of tubercle bacilli, there has been a tremendous stimulation of the body cells. There is the sudden outpouring of serum into the alveoli. The cell stimulation, however, has been excessive. As a result there are irritation and cellular destruction. The whole area undergoes caseation. This area may vary in size from that of the acinus, the unit of lung structure, to the entire lobe or even lung. The alveoli contain an albuminous exudate, much fibrin, and cellular elements. When caseation occurs, the alveolar network collapses so that the whole becomes a more or less homogeneous mass.

As might be expected, a patient with this type of lesion is sick and toxic. Inasmuch as all this caseous material must be sloughed out and got rid of before healing can occur, cough is severe and expectoration profuse. When finally the necrotic slough has been disposed of, there remains an empty cavity in place of the caseous tissue which has been expectorated. It is now that repair begins to predominate. Proliferative scar-tissue surrounds the area. Contracture of the scar occurs, with the subsequent distortion of the mediastinum or thoracic contents. It is this type, the end-stage of the above caseous-pneumonic tuberculosis, the so called chronic tuberculosis, that accounts for such a large proportion of our clinic attendance.

Clinically, this caseous-pneumonic type of tuberculosis is fairly easy to recognize. The onset is usually acute, the toxaemia and cough severe, and the expectoration profuse and loaded with tubercle bacilli. The physical signs are plentiful, with altered breathing, and many coarse

gurgling moist râles indicative of the breaking-down process that is taking place in the lung. X-ray shows a diffuse fuzzy shadowing, which is at first homogeneous but which later shows areas of high light where the caseous material has been sloughed out and the cavities remain. As scarring occurs, retraction and distortion appear. The cavities usually persist.

This caseous-pneumonic may be confused with the exudative type. Both are acute in onset. Both may be lobar or sublobar in extent from the start and may occur in any part of the lung field. The exudative type runs a benign course, and the patient is sick but a few days and then feels perfectly well, as he coughs but little and raises less. Tubercle bacilli are hard to find and the X-ray tends to clear often without leaving a trace of pathological involvement. The caseous-pneumonic patient, on the other hand, is sick and toxic, and remains so for a varying length of time. His cough is severe and his expectoration copious. Many bacilli are easily found, and X-ray reveals a lesion which ends in cavity-formation and extensive scarring. The following cases illustrate this type of process:

Case 3: Female, age twenty, housewife, one year before admission and immediately after her arrival in the United States from Porto Rico, caught a cold. The cough diminished but did not entirely disappear. Three months before admission, following parturition, the patient began having severe cough and expectoration. She was X-rayed, told she had pneumonia, and referred to the hospital. There was no history of any previous illness or of contact with tuberculosis. Examination on admission showed a sallow young woman, somewhat undernourished and obviously ill, with temperature 100.2°, pulse 122 and respirations 28. The signs in the lung were dulness over the right lower lobe, with some high-pitched râles after coughing. Breath-sounds were almost absent in this area. X-ray taken at this time (figure 7) showed marked impairment of illumination, with obliteration of lung markings on the right below the level of the 5th rib, anterior. Above this area to the level of the third rib, anterior, irregular mottling could be seen with an area of high light about one inch in diameter in the 4th interspace near the periphery. It was believed at this time that the patient had a pleural effusion with underlying lung involvement. Following admission, the patient's temperature ranged from 100.6° to 105°, and her pulse from 116 to 140. On bed-rest she slowly improved. Her temperature gradually fell to normal with an occasional peak to 100° or 101°. Her cough and expectoration diminished considerably. On routine tuberculosis care she continued to improve. She gained weight, and her temperature became normal and remained so. Her pulse

FIG. 8. CASE 3

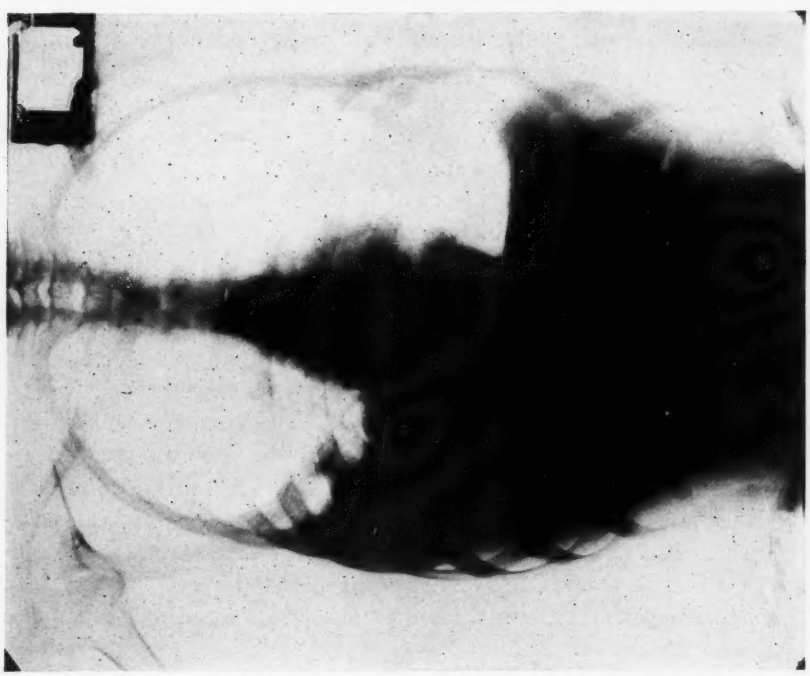

FIG. 7. CASE 3

was within normal limits. She still had a slight cough and raised a slight amount of sputum which was always loaded with tubercle bacilli. Nine months after admission there were still marked signs present. Bronchovesicular breathing and coarse moist râles were heard on the right below the fifth vertebral spine.

X-ray taken at this time (figure 8) showed some slight clearing in the diffuse haze at the right base. There was still extensive mottling present, however, and the cavity which was present on the original film still existed.

This case furnishes a very interesting comparison with case 2 of the exudative group. Both happened to show basal lesions of approximately the same extent yet how different has been the outcome. The exudative absorbs and clears: the caseous-pneumonic sloughs and cavitates. Our classification of this case on admission was *Caseous-Pneumonic Tuberculosis; Extent, Stage II; Symptomatology, Group C; Pleurisy with Effusion.*

Case 4: Female, born in United States, age fifteen, colored, one month before admission began to have a dry hacking cough which soon became productive. Blood-streaked sputum was noticed several times. She lost seven pounds during the four weeks before entrance to the hospital and felt listless and tired. No history of any illness obtainable. Mother and father died of tuberculosis.

Examination on admission revealed a well-developed and fairly well-nourished colored girl who did not appear acutely ill. Temperature 102.6°, pulse 140, respirations 25. Physical signs in the lungs consisted of dulness to the third rib and to the fourth vertebral spine, with bronchovesicular breathing and coarse moist râles to the fourth rib and to the sixth vertebral spine. There were occasional scattered sibilant râles throughout the left chest. The right lung was clear.

X-ray taken at this time (figure 9) showed a dense shadowing, extending out from the left root and involving a wedge-shaped area above the level of the third rib, anterior. The shadowing tended to be homogeneous except in its upper portion, where there were irregular areas of high light, there being one about an inch in diameter behind the clavicle. Irregular fluffy shadowing was present below this region to the level of the sixth anterior rib. Except for increased basal markings the right lung appeared clear.

The patient was put on bed-rest. Her temperature was irregular and varied between 100 and 103. Her pulse ranged as high as 120. She raised three to four ounces of sputum a day,—sputum that was loaded with tubercle bacilli. Five weeks after admission bronchovesicular breathing and coarse moist râles were present throughout the left chest.

X-ray taken at this time showed that there had been a massive spread throughout the left lung. This is well visualized in figure 10. Because of

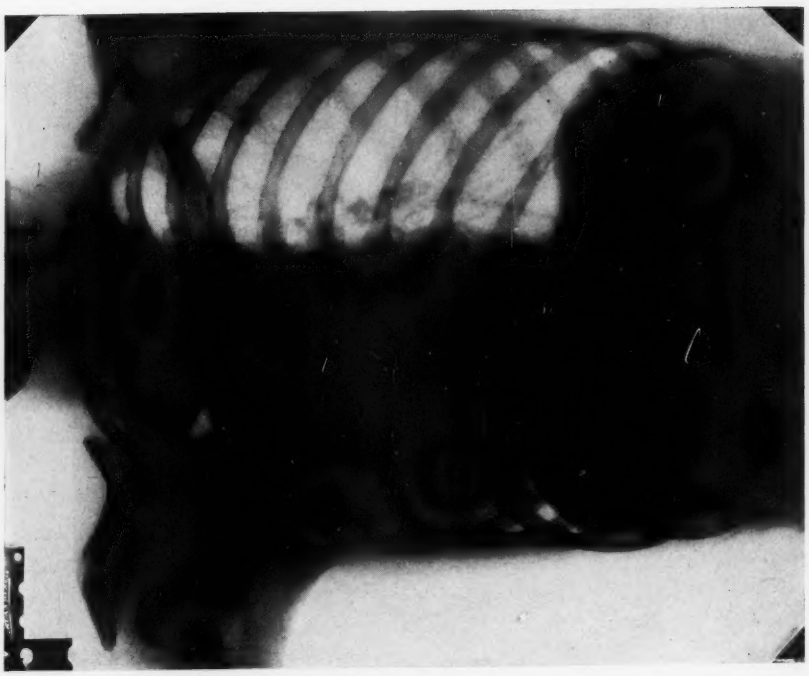

FIG. 10. CASE 4

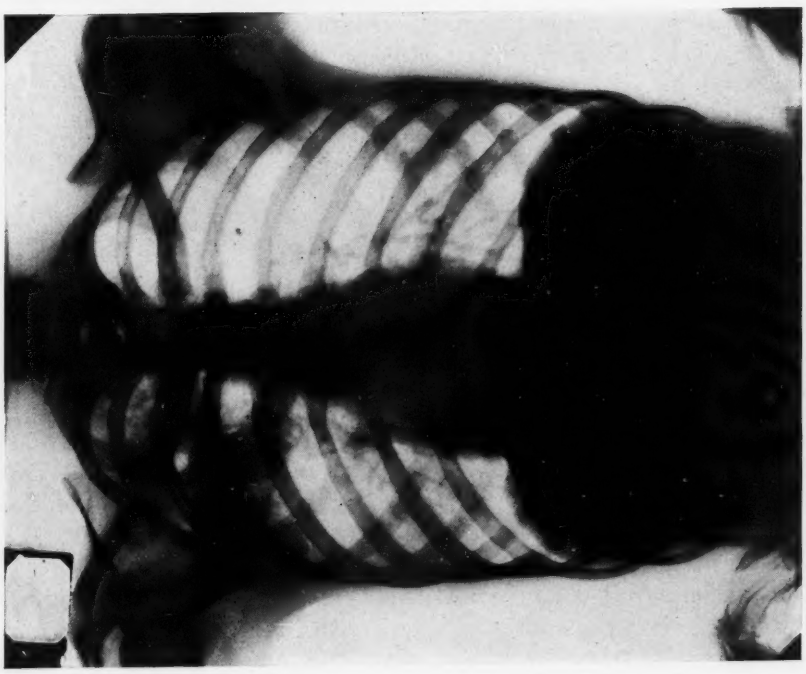

FIG. 9. CASE 4

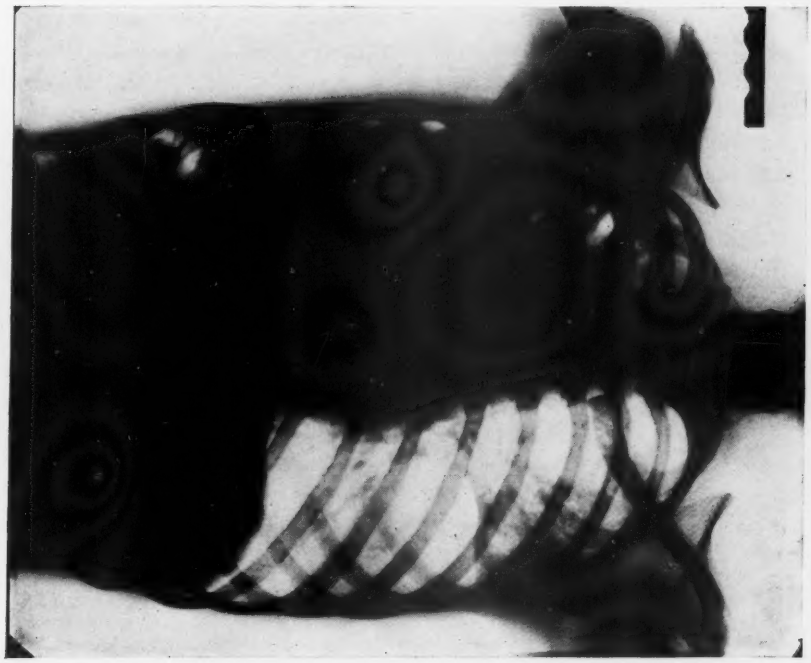

FIG. 11. CASE 4

FIG. 12. CASE 4

the evident lack of improvement it was felt that a phrenic neurectomy was indicated. Accordingly, two months after admission, the left phrenic nerve was avulsed. Immediately following the operation, the patient stated that she felt better. This improvement soon disappeared and one month later it was noted that the phrenic neurectomy had not helped the patient at all. X-ray taken at this time (figure 11) showed an increase in the extent of the high lights in the upper part of the left field, with a new extension out into the right lung.

Since then this patient's course has been progressively down-hill. She has run a spiking temperature as high as 103.4° and a pulse up to 120. She has a productive cough with sputum laden with tubercle bacilli. The caseated areas are being sloughed out as can be seen in figure 12 taken five months after admission. A comparison of this with figure 11 shows the tremendous increase in the areas of high light, indicative of the breaking-down process that is going on in the upper lung field.

This case illustrates the acuteness of the caseous-pneumonic type, its tendency to sloughing, and the usual toxaemia. Our classification on admission was *Caseous Pneumonic Tuberculosis; Stage II; Symptomatology, Group C.*

EXUDATIVE-PRODUCTIVE TUBERCULOSIS

As its name implies, the exudative-productive type of tuberculosis is a combination of both the exudative and the productive processes. The reaction at its onset is very similar to the caseous-pneumonic but it does not go on to softening and cavity-formation. The exudative and cellular elements are very slowly absorbed, finally leaving central strands of scar-tissue. There is, therefore, not as complete a clearing as is seen in the exudative type. The patient's symptoms too are more drawn out. The toxaemia is moderate and persists for a varying length of time; likewise the cough and expectoration.

X-ray shows densities of rather fluffy outline. As the collateral inflammation is absorbed, the haziness of the markings disappears, till finally only the central dense scar remains and remains permanently. The whole affair is spread over a period of months. The following cases illustrate this type of process:

Case 5: Male, born in Sweden, age twenty-seven, laborer, six weeks before admission developed a productive cough, which persisted. Three weeks later he coughed up 4 ounces of bright blood. Since that time he has felt weak and

has had occasional night-sweats. There was no history of any other illness or contact with tuberculosis.

Examination on admission revealed an adult male, not acutely ill, who appeared to have lost some weight. Temperature 98°, pulse 73, respiration 20. Physical findings were essentially negative except for the lung signs. On the right side anteriorly there was dulness to the third rib with bronchovesicular breathing and fine moist râles to the fifth rib. Posteriorly there were dulness and bronchovesicular breathing to the seventh vertebral spine except from the apex to the fourth vertebral spine where the breath-sounds were bronchial in character. Scattered medium and fine râles were present to the base. On the left bronchovesicular breathing was present from the second rib to the fourth vertebral spine with scattered fine râles posteriorly.

X-ray, taken on admission (figure 13), showed a dense homogeneous shadowing involving the right lung with a sharp lower border at the level of the interlobar fissure between the upper and middle lobes. There was an increase in the markings throughout the remainder of the right field. On the left there were increased peribronchial markings with mottled shadowing extending out from the root into the space enclosed by the third rib, anterior.

Following his admission the patient was put to bed and remained in bed fairly constantly. His temperature remained normal except for an occasional rise to 100°. Symptomatically he showed great improvement, so that five weeks after admission he stated that he felt better than he ever did. His weight, which on admission was 117, soon rose to 140 (normal). His cough and expectoration gradually subsided till he was coughing and raising practically not at all. On physical examination of the lungs there was definite evidence of improvement. Six months after admission there was bronchovesicular breathing on the right from the fourth rib to the sixth vertebral spine, with fine moist râles opposite the second to fourth vertebral spine, and, on the left, bronchovesicular breathing from the first rib to the third vertebral spine.

X-ray, taken at this time (figure 14), showed a shrinkage of the density in the right upper lobe, with a diminution of the mottling in the left upper lobe.

Since then the patient has shown steady progressive improvement both clinically and on X-ray. Figures 15 and 16, taken eight and twelve months respectively after admission, showed a gradual absorption of the homogeneous shadowing on the right, with a practically complete disappearance of the collateral haziness on the left, where only the central strands of scar remain. Eighteen months after entrance into the Tuberculosis Division of the Metropolitan Hospital examination of the lungs showed that there were bronchovesicular breathing and a few fine moist râles on the right to the third rib and to the fourth vertebral spine, with bronchovesicular breathing at the left apex. Figure 17 shows the X-ray appearance at this time. The homogeneous shad-

FIG. 14. CASE 5

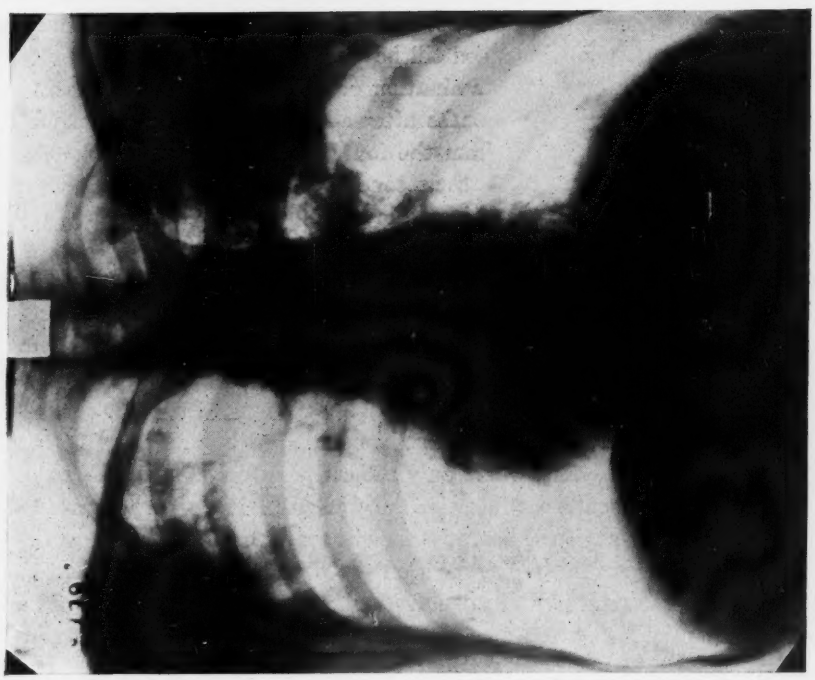

FIG. 13. CASE 5

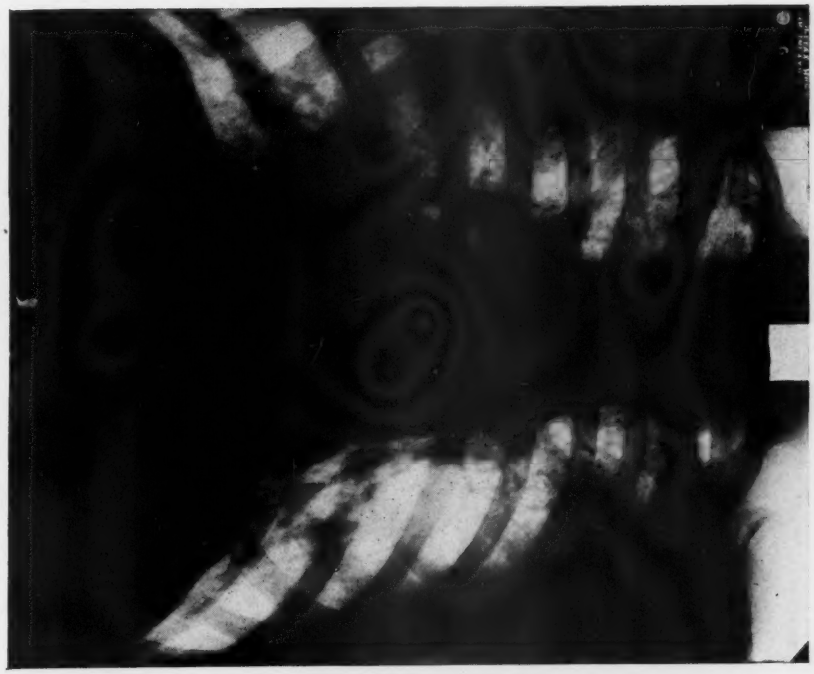

FIG. 15. CASE 5

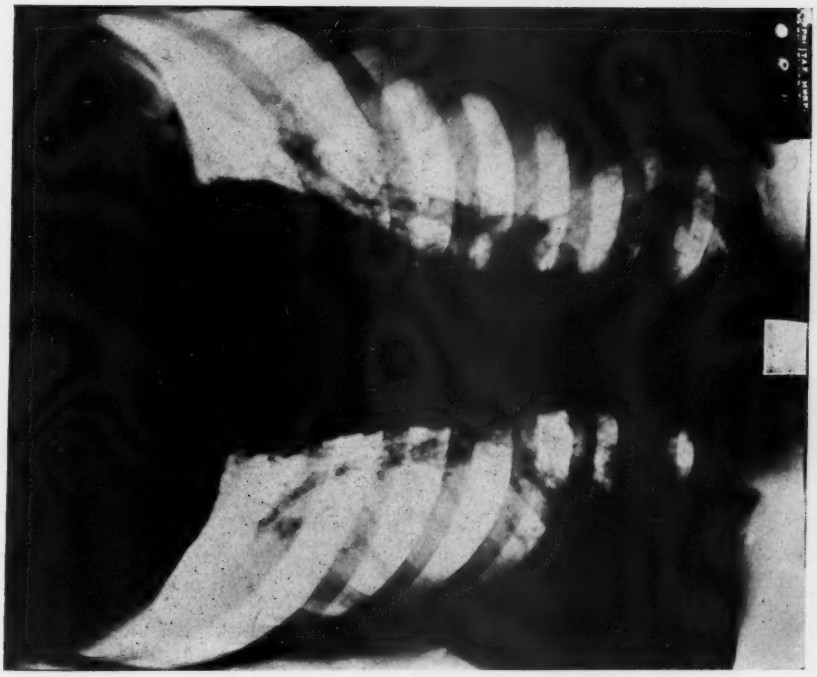

FIG. 16. CASE 5

owing in the right upper lobe has practically entirely disappeared and in its place can be seen linear strands of scarring. The disease on the left has undergone a similar process.

Since that time the patient's condition has remained stationary. His cough has disappeared. His sputum, which was positive for tubercle bacilli

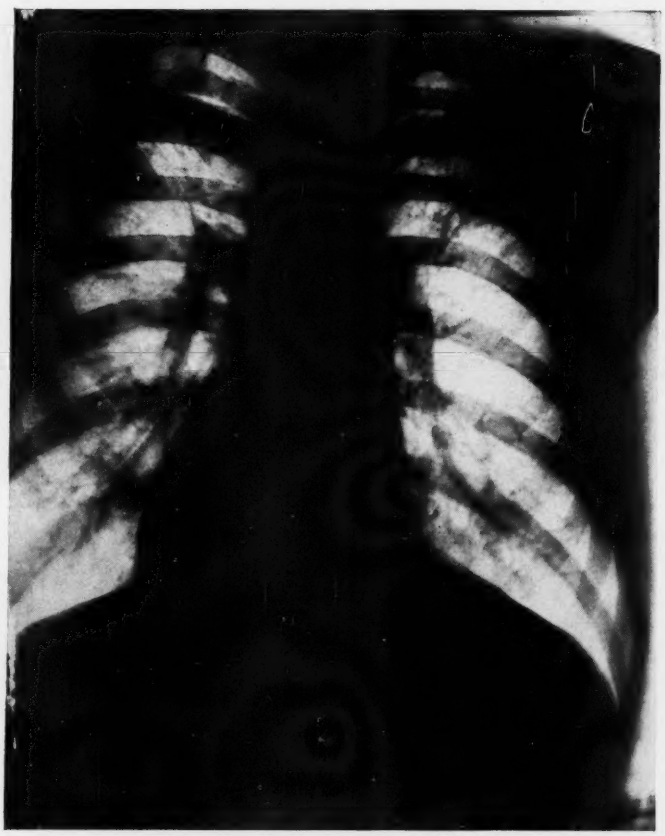

FIG. 17. CASE 5

on admission, has since then been negative. The patient feels well. On admission he was classified as *Exudative-Productive Tuberculosis; Extent of Lesion, Stage III; Symptomatology, Group A.*

Case 6: A young lady, twenty-six years of age, has been ill for two and a half months. She complained of her illness beginning with fatigue. She collapsed one day, perspiring profusely. She complained of no cough or expectoration.

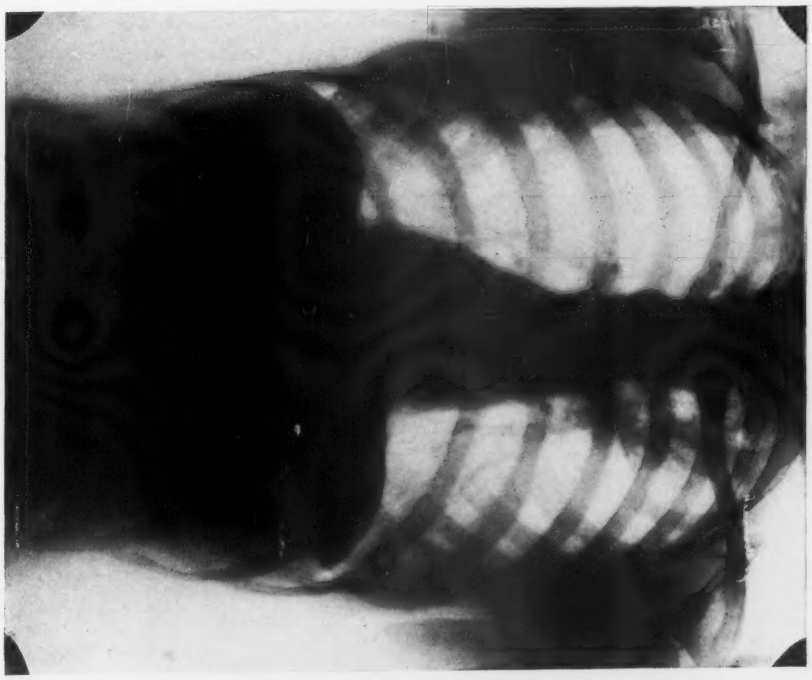

FIG. 18. CASE 6

FIG. 19. CASE 6

She had a temperature of 100° for five weeks, which then went above 103° where it remained for a few days. She was put to bed and, after remaining in bed for a few weeks, began to cough and expectorate. She was frequently hoarse, perspired at night and enjoyed only a poor appetite. She lost 20 pounds. Her history was irrelevant except for the fact that because of per-

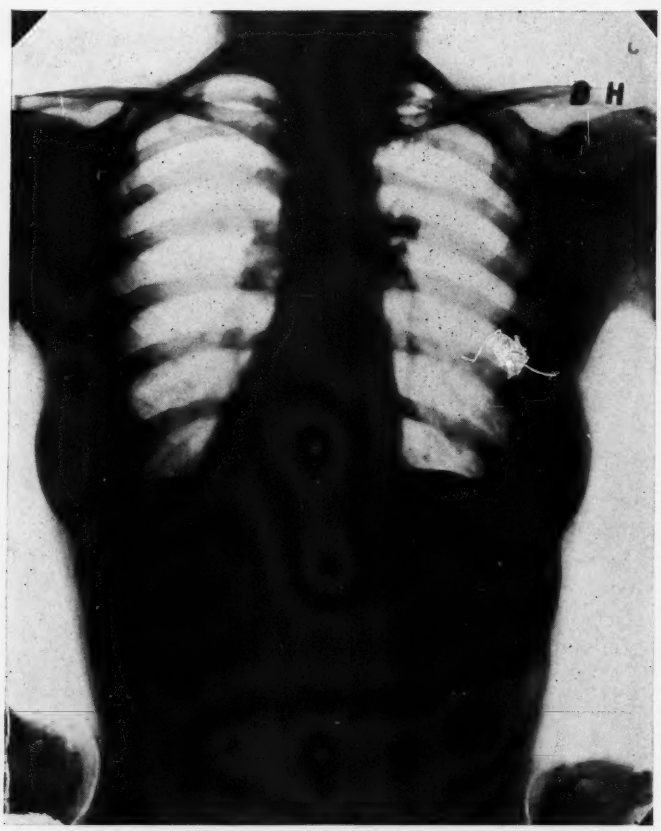

FIG. 20. CASE 6

sistent fatigue five years previously her thorax was X-rayed and reported negative for pulmonary diseases.

Physical examination of the right lung disclosed that the percussion note was very dull over the right upper lobe. The breath-sounds were bronchial over the upper lobe with an impression of cavernous breathing. No râles were heard. Over the left lung there was no modification of breath-sounds or râles. Tubercle bacilli were found in the sputum.

X-ray demonstrated a consolidation of the whole right upper lobe. There

was a high light which was annular in shape and resembled a cavity in the upper lobe. The course of the disease was as follows: The original picture was unfortunately lost. As mentioned above, the whole right upper lobe was involved. The patient was put to bed with no privileges as regards physical activity. Her temperature quickly dropped to normal. She coughed and expectorated less. All symptoms of toxaemia slowly disappeared and at the end of six weeks she gained 10 pounds. The physical findings were also changed. Breath-sounds were still altered in character but were now broncho-vesicular. No râles were heard.

An X-ray, taken about six weeks later (figure 18), showed marked absorption of the inflammatory process. After six months the patient lost her cough and expectoration. She had added another 20 pounds. An X-ray taken then showed further absorption of the process (figure 19). The following year she remained at home. She married and has been well ever since. Recently she returned for a check-up, to find out whether she could go through with a pregnancy. She had no complaints. Her X-ray (figure 20), taken four years later, showed a minimal proliferative process in the right upper lobe which followed the course of the paravertebral trunk.

This is an excellent example of the exudative-productive type of tuberculosis. There is a slow absorption of the inflammatory processes, leaving a little of the productive as a trace of the original infection. This patient would be classified originally as *Exudative-Productive Tuberculosis; Extent of Lesion, Stage II; Symptomatology, Group C.*

CHRONIC PROLIFERATIVE TUBERCULOSIS

If the superinfecting dose is small and the allergic reaction slight, then a low-grade proliferative response is the result. According to Aschoff, this process starts in the bronchial tree at the junction of the terminal bronchiolus with the *bronchiolus respiratorius*. The lumen of the tube is soon occluded. When this occurs, there is an absorption of air in the alveolar sacs, with the result that the pulmonary acinus becomes atelectatic and shrinks down to a small nodule around the proliferative focus. This constitutes the so called acinonodose type of tuberculosis of Aschoff. It is the result of small superinfecting doses in a relatively non-allergic tissue. When adjacent acini are involved, the lung grossly assumes a cirrhotic, scarred appearance. It is a type of process, which, because of its avascularity, is apt to give relatively few symptoms. The patient may have very few complaints, and may present himself only because of some complication, such as emphysema, or laryngeal or in-

testinal involvement. Because of its disseminated character and the surrounding emphysematous or normal lung tissue, physical signs may be surprisingly scant. Generally, however, there is altered breathing, dulness and fine high-pitched moist râles. X-ray usually shows a discrete type of shadowing, often nodular in shape. In fact, if the lesion be a disseminated one, it may be confused on the X-ray with the miliary type of tuberculosis. It is apt to start in one part of the lung field, usually the upper portion, and then through the course of years "browse" down through the remaining lung tissue. We have designated this type the "Chronic-Proliferative" type of tuberculosis. It is the type of process which seems little influenced by the various forms of treatment. If the process does not stop, it pursues a steady slow progression through the lung, the patient meanwhile feeling fairly well. It is the true chronic pulmonary tuberculosis. The terminal reaction in this type of case usually occurs with an exudative response. The tubercles may coalesce, and then ulcerate to form minute cavities which are usually not seen on the X-ray, probably because of their small size. The following are cases to illustrate this group:

Case 7: A young Italian boy, thirteen years of age, was examined as a contact. His younger sister had pulmonary tuberculosis. He had no complaints. Physical examination revealed no evidence of any altered breathing or râles in either lung.

The X-ray examination revealed a minimal nodular form of tuberculosis in the apex of the left upper lobe, as in figure 21. The patient was sent to the country to be away from the open case at home. His weight increased and, when his sister was removed to one of the local hospitals, he went home. Sixteen months later he was brought in for another examination. His general condition was excellent. He complained of no cough or expectoration and had gained 10 pounds. Physical examination revealed no changes from the normal. His X-ray (figure 22), however, showed an increase in his pathological involvement. This had progressed down to the second rib anteriorly and appeared to occupy the first interspace.

The mother was cautioned and the child carefully watched. There were no symptoms and his temperature and pulse-rate were normal. He felt well, and was hard to manage in regard to his play with other children because of his well-being. He was again X-rayed ten months later, when another increase in involvement was noted (figure 23). The lesion extended beyond the second rib anteriorly into the second interspace. The patient appeared in excellent health and physical examination revealed no changes in his lungs. The boy

FIG. 21. CASE 7

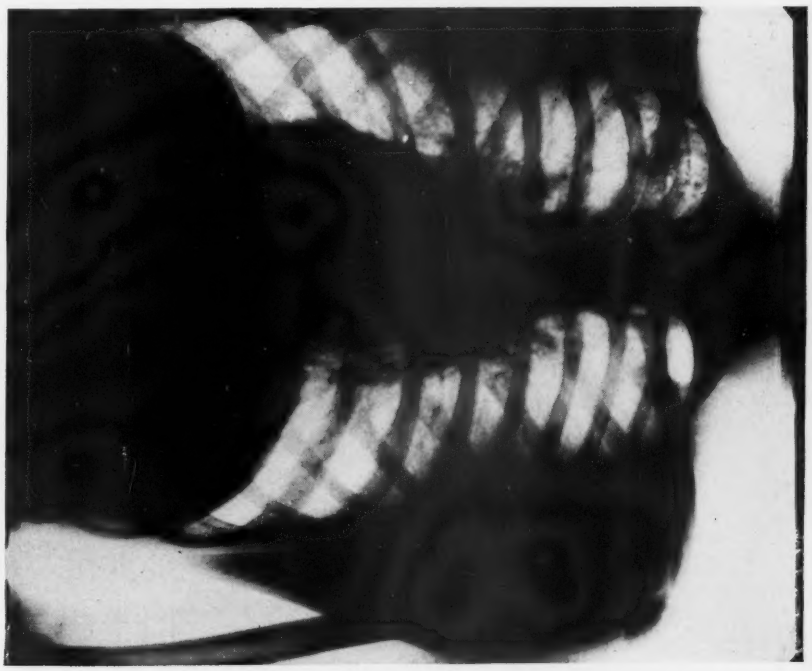

FIG. 22. CASE 7

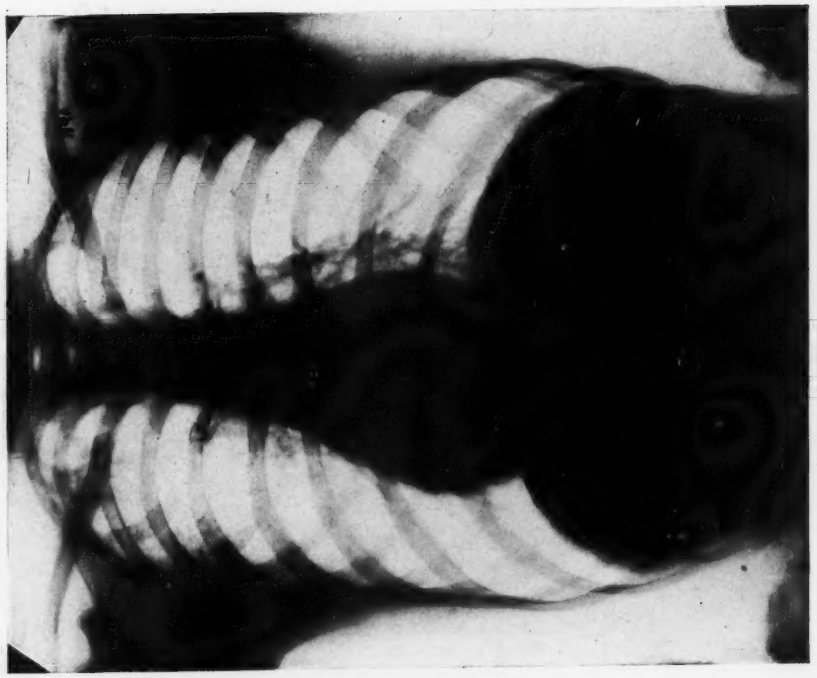

FIG. 24. CASE 7

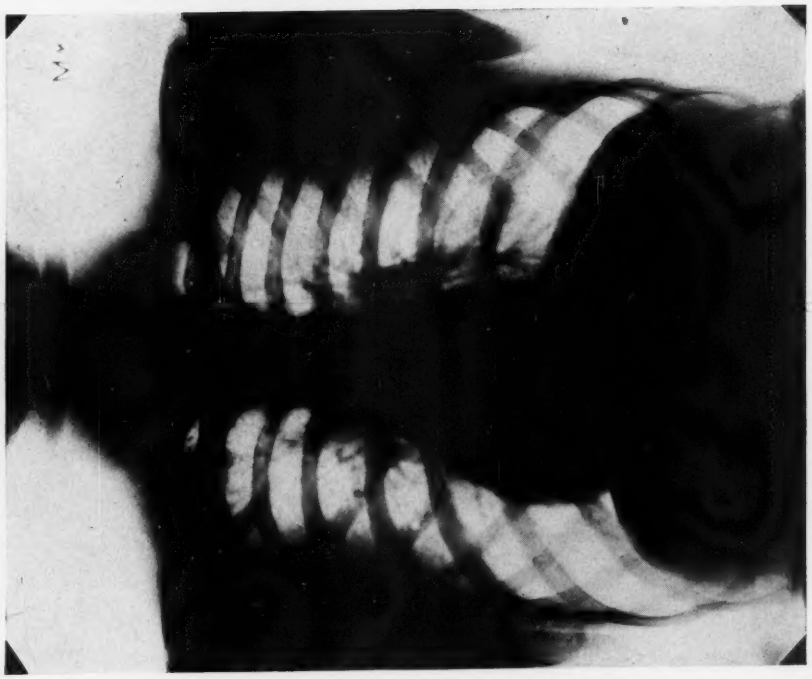

FIG. 23. CASE 7

was not brought in again because of his excellent health for over fourteen months. He had no complaints and had gained 39 pounds in the past three years. Physical examination again revealed no abnormal findings. The X-ray (figure 24), however, showed further extension of the process. The lesion had extended down below the third rib into the third interspace. The pathological changes above had also increased in amount. This case illustrates one of the types of reaction of the chronic proliferative form of tuberculosis, the disease through the course of years "browsing" down through the lung field, the patient meanwhile enjoying good health. We believe that this is the usual course of most of the chronic proliferative cases that progress. This case could be classified when first seen as *Chronic Proliferative Tuberculosis; Exient of Lesion, Stage I; Symptomatology, Group A.*

Case 8: A young Japanese, twenty-five years of age, has been ill for the past five years. He complains of occasional cough, with slight expectoration which is usually accompanied by some blood-streaked sputum. He has no other complaints. He comes to the clinic only because of the haemoptysis.

Examination of the lungs revealed occasional moist râles, heard over the upper lobes of both lungs, but, as a rule, no adventitious sounds were heard. The breath-sounds were emphysematous in character.

X-ray (figure 25) reveals a small nodular form of tuberculous infiltration involving the upper portions of both upper lobes. The process has extended slowly in the past year. This is an excellent example of the chronic proliferative type. This case may be classified as *Chronic Proliferative Tuberculosis; Extent of Lesion, Stage II; Symptomatology, Group A.*

Case 9: Male, born in Russia, age sixty-three, laborer. Nine years before admission had a slight cough, with blood-streaked sputum and some pain in the left chest. Following this he felt very well till four years before admission when he began to cough and raise. Recently this cough and expectoration became more severe. Weakness, gradual loss of weight and pain in the left chest were noted, so that finally the patient was forced into the hospital. There was no history of any other illness or of contact with tuberculosis.

Examination on admission revealed a middle-aged man, somewhat thin and undernourished but not acutely ill, with temperature 98.4°, pulse 84 and respirations 22. Physical signs in the lungs consisted of dulness and bronchovesicular breathing over the right upper lobe, with scattered medium moist râles. There were dulness and bronchovesicular breathing on the left from the second rib to the fourth vertebral spine.

X-ray, taken at this time (figure 26), showed an extensive nodular type of scarring. This nodular scarring tended to coalesce at the right apex, produc-

FIG. 26. CASE 9

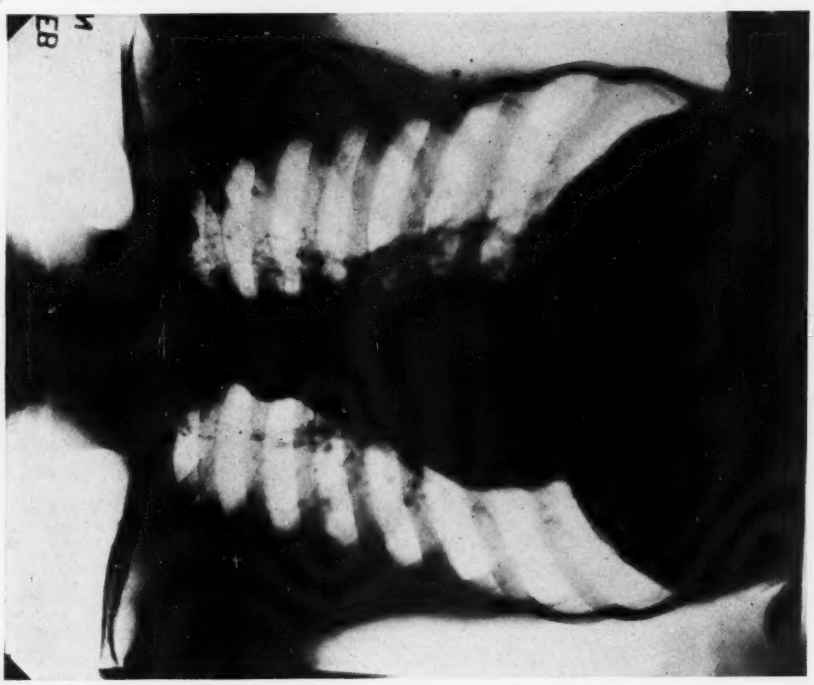

FIG. 25. CASE 8

ing a dense cirrhotic appearance. This patient is still on the ward, five months after admission. His cough and expectoration have diminished. He has gained 5 pounds. His sputum is persistently positive. His X-ray appearance has not changed. He has been classified as a case of *Chronic Proliferative Tuberculosis; Extent of Lesion, Stage III; Symptomatology, Group B.*

SUMMARY

From the above description it can be seen that we believe that there are four main types of tuberculosis, the exudative, the caseous-pneumonic, the exudative-productive and the chronic proliferative. These four types should form the basis of our classification. The anatomical extent, such as minimal, moderately advanced, or far advanced, can be applied as at present to each of the four types, with these exceptions: first, cavity shall not automatically classify the case as far advanced; second, complications shall be listed separately and shall not influence the pulmonary classification. The symptomatic classification, "a," "b" and "c", are to be continued as at present. Thus, a case might be listed as *Exudative III* or as *Caseous-Pneumonic II C*. This classification immediately gives us much additional and necessary information. It tells us that the stage-III case will be completely well in a comparatively short time while the *Caseous-Pneumonic II* is going to have a long struggle. It also will give some value to series of cases that are reported, and will enable one to determine intelligently the value of therapeutic measures,—something which is impossible at the present time. For if an exudative and a caseous-pneumonic case can both be classified as far advanced, without any reference to their totally different pathological process, as is the case now, how can one determine the result of any therapeutic measures? The exudative will recover regardless: the caseous-pneumonic will not. This simple error, engendered by our present classification, may serve to explain the different results obtained by different observers with the same therapeutic methods. Frequently cases are seen which combine two different types of pathological process; thus a person may have an apical caseous-pneumonic and a basal proliferative. It is only through a competent understanding of the underlying pathological process that one can intelligently classify the case. We believe our proposed modification of the existing classification supplies this urgent need.

APPENDIX

In the following pages we have attempted to summarize the viewpoints of the various authors on the question of classification of tuberculosis:

1: Bard

A. Formes parenchymateuses
  1. Forme abortive
  2. Formes progressives
    a. formes caséeuses
      1. lobaire
      2. extensive
    b. formes fibro-caséeuses
      1. extensive
      2. congestive
      3. cavitaire ulcéreuse localisée
      4. cavitaire stationaire
      5. ulcéro-fibreuse
    c. formes fibreuses
      1. pneumonie hyperplastique
      2. sclérose dense
      3. sclérose diffuse et emphysemateuse

B. Formes interstitielles granuliques
  1. Granulie généralisée
  2. Granulie pulmonaire suppuree
  3. Granulie migratice
  4. Granulie discrète

C. Formes bronchiques

D. Formes post-pleurétiques

(Various forms under B and D not enumerated)

2: V. Rosthorn and A. Fränkel

A. Apical processes, unilateral or bilateral

B. Upper-lobe processes, unilateral or bilateral
  1. infiltrative
  2. cirrhotic
  3. cavernous

C. Upper-lobe processes with changes in middle or lower lobes.

3: E. Albrecht

A. Qualitative
  1. Cirrhotic (with or without cavitation)

2. Nodular (with or without cavitation)
3. Caseo-pneumonic (with or without cavitation)

B. Quantitative
1. Isolated foci, particularly of upper lobe
2. Extensive upper lobe processes
   a. unilateral
   b. unilateral with extensive lower-lobe process of same side
   c. with small or extensive tuberculosis of other side
   d. upper-lobe process of both

C. Classification according to presence or absence of complications
1. Emphysema, bronchiectasis, etc.
2. Gastrointestinal tuberculosis
3. Larynx
4. Constitutional disturbance such as fever, anaemia, etc.

4: L. Brown

A. Classification on admission
1. Incipient: slight pathological changes and symptoms
2. Moderately advanced
3. Far advanced

B. Classification on discharge
1. Apparently cured
2. Arrested
3. Improved
4. Unimproved

C. Classification of ultimate results
1. Cured
2. Well
3. Arrested
4. Improved
5. Progressive
6. Death

5: Buttner-Wobst

A. Indurative
B. Nodular
C. Caseous

There are mixed forms in all of these. Extent and location of lesion is described. He noted that only indurative and nodular heal.

6: W. L. Rathbun

Lesions	*Symptoms*
A. Incipient	A. Slight
B. Moderately advanced	B. Moderate
C. Far advanced	C. Severe

7: A. Bacmeister

A. Progressive tuberculosis
   Stationary
   Inclining to latency
   Latent
B. Indurative
   Disseminated
   Pneumonic
C. Open and closed tuberculosis
D. Extent of lesion

8: K. Nikol

A. Productive
   1. Interstitial
   2. Acino-nodose
   3. Cirrhotic
B. Caseo-exudative
   1. Bronchopneumonic
   2. Lobarpneumonic

SECONDARY CHANGES	BACILLI	REACTION	EXTENT

9. A. Schmincke

A. Acute haematogenous miliary (may have associated exudative pneumonia or intraälveolar tubercles. Small groups of miliary caseous tubercles in acini.)
B. Nodular tuberculosis, intracanalicular
   1. Nodular proliferative
   2. Nodular exudative (pneumonic)
C. Confluent processes
   1. Cirrhotic: result of proliferative lesion
   2. Confluent pneumonia

10: L. S. T. Burrell: Classification based on life history of patient

A. (1) Hospital stage
   (2) Sanatorium stage
B. Stage of maximum improvement
C. Stage of decline

11: Brown, Heise and Sampson

A. On admission
   1. Minimal pathological changes and symptoms
   2. Moderate pathological changes and moderate impairment of function
   3. Far advanced pathological changes and severe impairment of function
   4. Miliary

B. On discharge
   1. Apparently arrested
   2. Quiescent
   3. Improved
   4. Unimproved
   5. Died

C. Ultimate results
   1. Apparently cured
   2. Well
   3. Arrested
   4. Improved
   5. Progressive
   6. Dead

12: Waters and Amberson

A. Minimal
B. Moderately advanced } by X-ray
C. Far advanced

13: E. Romberg

A. Exudative pulmonary tuberculosis
   1. Bronchopneumonic
   2. Pneumonic

B. Proliferative (productive) tuberculosis
   1. Pure proliferative
   2. Proliferative cirrhotic (cranio-caudate)

C. Cirrhotic
   (No type pure)

14: A. Fraenkel and S. Graff

A. Quantitative
   1. Unilateral, bilateral
   2. Location

B. Qualitative
   1. Cirrhotic, cirrhotic-nodular, nodular-cirrhotic
   2. Acinous-nodous

3. Lobular exudative and caseous
4. Lobar caseous

C. Criteria
1. Closed or open tuberculosis
2. Fever

They emphasized the importance of complications in prognosis.

15: A. Pissavy

A. Les tuberculoses granuliques ou septicemiques
B. Les tuberculoses pneumoniques: three stages: splenization, seroleucocytic exudate, resorbs; hepatization, fibrinoleucocytic exudate, may not caseate, but resorb and fibrose; caseation.
1. Pneumonie caseeuse; three stages may be present here
2. Splenopneumonie; resorbs completely
3. Bronchopneumonie; all stages present
C. Les tuberculoses nodulaires (discrete and disseminated)
D. Les tuberculoses bronchitiques et emphysemateuses
E. Les tuberculoses pleurales

Pissavy's scheme is based on Bard's. It is simpler than Bard's and more in accordance with our own.

16: Rockhill, Craddock and Amberson

Lesions	*Symptoms*
A. Minimal	A. Slight
B. Moderately advanced	B. Moderately severe
C. Far advanced	

Schema for subsequent observations

A. Apparently cured	E. Improved
B. Arrested	F. Unimproved
C. Apparently arrested	G. Died
D. Quiescent	

17: F. M. Pottenger

Group I: Symptoms due to toxaemia
Group II: Symptoms due to reflex causes
Group III: Symptoms and syndromes due to process *per se.*

Pottenger thought that extensiveness of lesion was not the most important factor, but reaction of patient.

18: H. Ulrici

Group I: Exudative, with or without cavitation

a. Caseous lobar

b. Caseous lobular

Group II: Productive, with or without cavitation

a. Nodose

b. Cirrhotic

19: Ranke

A. Primary complex: primary effect with lymphogenic metastasis in regional lymph nodes.

B. Secondary stage: dissemination by

1. Blood
2. Lymph
3. Contact and bronchi

C. Tertiary stage: spread by contact and bronchi

Ranke mentioned importance of biological principles and hypersensitivity and immunity in tuberculosis.

20: Nicol

A. Haematogenous (miliary)

1. Pure interstitial
   a. pure productive
   b. tuberculous exudative
2. Acinous "*Ausscheidung's*" (secretory) miliary tuberculosis
   a. acinous productive
   b. acinous exudative

B. Bronchogenic

1. Productive
   a. acino-nodose
   b. cirrhotic
2. Exudative
   a. caseo-bronchopneumonic
   b. caseo-pneumonic

Nicol also included in his classification the extent of lesion, whether open or closed, cavitation, reaction of patient.

21: Beitzke (in Aschoff)

A. Primary: pure or with secondary

B. Secondary

1. Productive
   a. disseminated miliary

b. acinous
c. acino-nodose
d. cirrhotic
2. Preponderantly caseo-exudative
a. acinous caseo-pneumonic
b. lobular
c. lobar

22: Lydtin

200 cases (postmortem)
35 inactive, cirrhotic, apical
112 cirrhotic-proliferative
53 exudative: three-fifths exudative are end-stage of cirrhotic proliferative

23: Turban

Turban's newer classification not only respected extent of lesion but
1. Stage of anatomico-biological evolution after Ranke
2. Pathological anatomy after E. Albrecht, with X-ray to decide
3. Clinical features

24: Bernard

A. Chronic
1. Ulcero-caseous, extensive
2. Ulcero-caseous, localized
3. Ulcero-fibrotic, extensive
4. Ulcero-fibrotic, localized
5. Bronchitic tuberculosis with emphysema

B. Acute
1. Caseo-pneumonic
2. Galloping phthisis
3. *"Granulie"*
4. Cortico-pleuritic
5. Pleurisy

25: Sternberg

A. Three stages of extent
B. Dynamics of disease
1. Practically healthy
2. Compensated
3. Subdecompensated
4. Decompensated

If X-ray shows qualitative type of lesion, the type may be mentioned.

26: Cummins

A. History and duration of disease into acute (less than two years) or chronic

B. Anatomical extent

1. Minimal
2. Moderate
3. Far advanced

C. Constitutional balance into

1. Resting febrile
2. Ambulant febrile
3. Ambulant afebrile

27: Reisman

Group I: History of contact with negative tuberculin test

Group II: History of contact, positive tuberculin; no evidence of disease, no lymph nodes

Group III: Incipient, and history of contact, positive tuberculin, slight tracheobronchial lymph-node enlargement by X-ray

Group IV: Massive tracheobronchial enlargement, fibrosis, calcification, positive tuberculin

Group V: Parenchymatous infiltration with caseation

28: Bard

This later classification of Bard's is very much like his earlier one in 1901.

29: Neumann

Because the same anatomical process might give rise to totally different pictures and because the same picture of the disease might be the end-result of totally different anatomical processes, Neumann had advanced this clinical classification:

A. Cavities with clinical signs

B. Cavities without classical signs, and cavities complicating *fibrosa densa* and *diffusa* (classical and silent)

C. Exudative-bronchopneumonic

1. Reinfection infiltrate; may caseate
2. May resorb; splenopneumonic
3. Associated with *fibrosa densa* and *diffusa*, ulcero-fibrosa

D. *Fibrosa-densa, fibrosa-diffusa*

E. Pulmonary tuberculosis with no manifestation except pleural thickening

30: Toinon

In this report there is contained a summary of several popular French classifications.

31: Neumann

Neumann in the latest edition of this book uses the Bard-Piery classification with the principles laid down by Ranke as the basis for his own.

A. Reinfection tuberculosis

1. *Fibro-casea communis*, Ranke IV schema; organ-limited tuberculosis (*früh Infilträt*)
2. *Tuberkulose cavitarid stationarid*
3. *Tuberkulose abortiva*
4. Repeated pleuritis

B. Haematogenous; Ranke III schema

1. Miliary, disseminated
2. Virulent proliferative (11 forms)
3. Lesser-circulation tuberculosis
4. Bland proliferative

C. Generalized tuberculosis as direct result of primary infection; Ranke II schema; three modes of dissemination: (1) *phthisis caseosa;* (2) chronic puberty tuberculosis

D. Primary complex; Ranke I schema

E. Exudative pleuritis (3 forms)

F. Processes not fitting into Ranke schema

1. Superficial bronchitis
2. Tuberculous peribronchitis

G. Pneumonic processes by tuberculosis (perifocal)

1. Congestive of Bard
2. Gelatinous
3. *Pneumonia hyperplastica*

H. Acute malignant tuberculosis

1. Acute bronchopneumonia
2. *Bronchitis capillaris*

I. Masked tuberculosis

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THE CLINICAL APPLICATION OF ARTIFICIAL HELIOTHERAPY[1]

HENRY STUART WILLIS AND JACOB COHEN[2]

Heliotherapy has become a veritable panacea to both the layman and the physician. It has been used as a stomachic and a tonic; in hypotension and in hypertension; in rickets, anaemia, pneumonia, diseases of the skin, arthritis, adenitis of varied type, tuberculosis in many forms, bronchial asthma, hay fever, urticaria, infected wounds, suppurating and nonsuppurating wounds, dental caries and neurological disorders; during convalescence from disorders of several sorts, and in a host of less specific maladies. More! Some of us have found in ultraviolet light a cure for these diverse diseases. That it is a valuable therapeutic agent cannot be gainsaid, but we are in error when we apply it uncritically and without control to all sorts of conditions, and attribute whatever improvement that may appear in the patient's ailment to this agent.

Most thoughtful observers agree that there is need to sift the claims and to seek a rational basis for the therapeutic application of ultraviolet radiation. Many physicians, who have known that no single remedy can conceivably be a specific for such an array of diseases of widely diverse nature, have desired to know in what conditions they might apply ultraviolet light rationally and with reasonable expectation of benefit to the patient. To enquire into certain aspects of this question has been the aim in the prosecution of the study we have begun.

Any acquaintance with the literature or much practical experience with this type of therapy will teach us that, in the treatment of certain diseases, ultraviolet light is of so great value as to be a specific. This is shown by perfectly acceptable evidence that it leads to definite photochemical changes which are specific and curative in rickets, and by fairly good evidence that, in certain forms of tuberculosis (particularly enteritis), it is often of great therapeutic avail; also, there is some work to show that it may be of help in the treatment of tuberculous peritonitis,

[1] Read before the Johns Hopkins Medical Society, May 12, 1930.

[2] From the Kenneth Dows Fund for the Study of Tuberculosis, of the Johns Hopkins University and Hospital, Baltimore, Maryland.

adenitis and osteitis, and that in many instances it produces a gratifying tonic effect. However, we do not believe that the evidence which has been brought forth so far is convincing as to its efficacy in other conditions.

At the Johns Hopkins Hospital we inaugurated our light clinic two years ago in a modest way with one lamp. During the first year we had a total of nearly 75 patients and at the end of that time we made an effort to evaluate the results. But we soon faced the issue of having no controls with which to compare the treated cases. We were able to gather certain impressions: namely, that in general (1) the arthritics and those with osteomyelitis received no benefit; (2) those with nonspecific cervical adenitis received prompt subsidence of their symptoms; (3) those with suppurative (fluctuant) tuberculous adenitis got no beneficial results, although in this group many with sinus-formation were materially aided; and (4) those few with tuberculous peritonitis and gynaecological tuberculosis did well.

No satisfactory data on nontreated cases of similar disease were available for comparison and control. Therefore, we were unable to really appraise the results or to honestly and critically know whether the light had been responsible for the improvement noted. It occurred to us that the actual efficacy of heliotherapy is sufficiently uncertain and obscure to justify us in deliberately withholding it from patients in whom it may possibly have been of therapeutic value. We would certainly not be justified in withholding ultraviolet light in rickets, because it is a specific remedy in this disease. We should hesitate to withhold it in tuberculous enteritis or peritonitis, because the evidence indicates that, although it is not a specific, ultraviolet light may be a therapeutic measure of first importance in these affections and usually leads to a marked regression of symptoms. However, we would be hard put to it to find any other disease which light so unequivocally benefits that its lack of application would *be known* to deprive the patient of what might even be termed the "method of choice" in the treatment of his condition. Clausen (1) has recently emphasized just this point in her review of the subject. The observations of Mackay (2) certainly lend support to the contention that it is only by well-controlled clinical data that we will arive at a knowledge of what ultraviolet light may actually accomplish.

Therefore, after the first year we planned to turn the light clinic into an experimental station by providing control patients who should be comparable to the treated group in every way but for deprivation of the

short ultraviolet waves,—waves ordinarily used in artificial heliotherapy. This we did by interposing a screen of plate glass just under one of the burners. Alternate patients, irrespective of race, sex or diagnosis, were placed under this dummy light. (We should use the term "dummy" with reservation in this connection. Plate glass screens out the shorter ultraviolet waves in the zone which is specific for rickets but, as we shall comment upon more in detail later, it transmits long ultraviolet rays and visible rays, the therapeutic effect of which we know nothing.)

There are a few observations and criteria that are germane to this study which should be considered briefly. In the first place, all conditions, save for the interposition of the screen, were maintained as nearly as could be in the two groups of cases. The two lights were kept in the same room and were separated by heavy draw-curtains; the same nurse took care of both groups of patients and she herself did not know anything about the experiment except that one lamp had a *special* screen; the initial exposure and the rate of increase were given to all patients and the same length of exposure for the front and for the back. The possible psychic effect of the treatment was borne in mind.

Second, dosage of ultraviolet light is a matter of much more importance than it is generally thought to be. All too often a series of lamps which are procured and put to work are presumed to have the same capacity. This, however, is not always the case. But the rate of deterioration of the lamps may vary tremendously, as Dr. Janet Clark has found in the lamps under her observation.[3] Indeed, our last two burners were new (and presumably) standard and comparable in October, 1929. But by February, 1930, one lamp emitted three times as many short ultraviolet rays as the other, although both of them had burned approximately the same number of hours.

In the third place, the degree of exposure is significant. Our routine has been to begin rather arbitrarily with small exposures which were gradually increased. In the beginning of the treatment, the patient was 36 inches from the lamp and the duration of his exposure was two (sometimes three and four) minutes front and back. *All exposures were general.* The duration was lengthened three (sometimes four and five) minutes at each of the triweekly treatments, until at the end of four weeks 30 to 45 (or even 60) minute exposures (both front and back) were given. Usually, when the maximal exposure was reached, we would

[1] Personal communication.

gradually lower the lamp and thus shorten the distance, which was sometimes reduced to 18 but generally to 24 inches. It was realized that, when the light is near the patient, the portion of the skin immediately beneath it is intensely exposed while the remote parts, that is, head and feet, receive only slight exposure from the tangential rays.

Local disease was practically always in the field of exposure in this scheme. Treatment continued in some instances for only a few exposures, in several for as long as one and one-half years. But in all instances the same routine was observed irrespective of whether the screen were interposed or not. No patient is included in the series who was under treatment less than one month.

Fourth, the source of light was the Hanovia Chemical Company's Alpine mercury-vapor-quartz lamps, which were generously loaned by this company for several months' use. Direct current of 110 volts was used. The lamps were not in series but each was plugged in separately. The screen was made very simply from an aluminum dishpan, the bottom of which had been reamed out, and replaced by a disc of plate glass which was secured by cleats. The pan was suspended by wire to the dome containing the burner. This was so made as to be readily removed or attached. It is illustrated in figure 1.

It is recognized that the screen transmits ultraviolet rays of certain lengths. Ultraviolet light falls into the range lying between 1850 and 3800 Angstrom units. The majority of ultraviolet rays in ordinary sunlight are in the neighborhood of 2900 units. The rays in the zone from 2900 to 3100 Angstrom units are those which prevent rickets, which produce sunburn and suntan, and which lead to a normal growth of babies (Goodman). We know that these do not penetrate glass. We know but little of the therapeutic effect of the longer ultraviolet rays. We know that the longer waves penetrate human skin somewhat more deeply than shorter rays and that it is unlikely that any of them penetrate deeper than 3 mm. (Anderson and Macht (3)). We know that the skin of the colored race absorbs much more ultraviolet rays than that of whites. It is thus clear that, in interposing the screen, we are probably affecting only one of several factors. In doing so we allow the transmission of the long ultraviolet rays, the visible rays and some infrared rays, and these may exert therapeutic effects that we as yet know nothing about.

Finally, the patients were divided almost equally between white and colored. They were sent to us from several different services and they represented a variety of diagnoses, for the types of disease varied rather

widely. Adenitis, mostly tuberculous, was the most frequent diagnosis. In addition to tuberculosis of the cervical lymph nodes, numerous cases of tuberculosis of the tracheobronchial lymph nodes, of the skin (erythema induratum), peritoneum and genitourinary system were treated. Chronic arthritis, chronic infectious arthritis, and osteomyelitis were all represented in fair numbers. A few cases of secondary anaemia and postoperative convalescence completed the list.

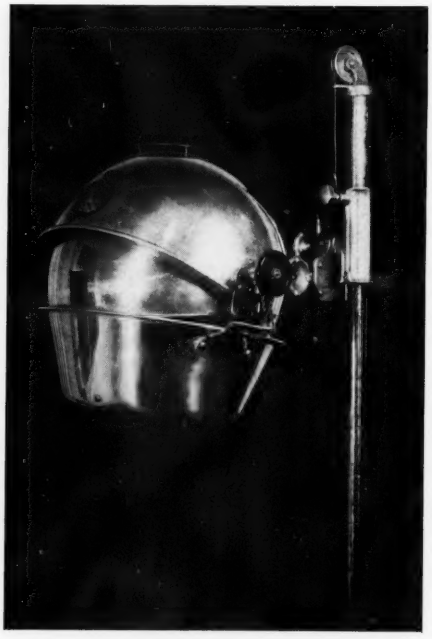

FIG. 1. PHOTOGRAPH OF LAMP WITH SCREEN ATTACHED

Description is given in text

The patients were uniformly given a careful, thorough, general physical examination, which included such special examinations as might be indicated in the individual case; for instance, laryngological and dental survey in the patients with cervical adenitis. They were reexamined at monthly intervals during treatment. All of them had an initial and a final X-ray of the chest as well as special X-rays when these were indicated.

We put forth a special effort to tie in the originating clinic with the light clinic so that the patient could be closely followed in both depart-

THE JOHNS HOPKINS HOSPITAL

REFER SLIP FOR LIGHT TREATMENT

History No._____ Date_____

DETACH AND GIVE THIS PART OF SLIP TO PATIENT TO TAKE TO ROOM 4 FIRST FLOOR DISPENSARY BUILDING.

Date_____

Name_____ No._____

Diagnosis_____

Treatment of_____

Return Date_____

ON THIS DATE PATIENT MUST RETURN TO ORIGINAL CLINIC FOR EXAMINATION AND RECEIVE NEW PRESCRIPTION BEFORE TREATMENT WILL BE CONTINUED.

LIGHT TREATMENT CLINIC Dr._____

Clinic_____

DO NOT FILL IN SPACE BELOW THIS LINE

Area to be exposed_____

Anterior_____

Time

Posterior_____

Rate of Increase_____

Maximum Exposure_____

Length of Ray_____

No. of treatments per week_____

Dr._____

FIG. 2. PHOTOGRAPH OF REFER SLIP

Description is given in text

ments. This was of paramount importance, for, if it were not done, the patient would soon be lost to the originating clinic. The mechanism of this scheme was carried out by the use of the form illustrated in figure 2.

Altogether we have treated 138 patients, but of this number 44 were insufficiently treated, as will be seen in the following tabulation:

Total number of cases

Total patients treated in ultraviolet light group	91
Total patients treated in control group	47
Total patients treated in series	138
Total patients insufficiently treated	44
Total patients under discussion	94

Such an array of patients is small,—so small in fact as to seriously modify any conclusions that might otherwise seem justified. No one is more cognizant of this fact than we are. But what we hope to do is to report work in progress and to evaluate it as it stands at present rather than to arrive at established conclusions. Whatever deductions that may be forthcoming should be regarded only as indications to be followed further or at best as tentative conclusions.

RESULTS

What of the results? The number of cases is too few for statistical analysis. Therefore, we have chosen to simply list the cases in the two lots as either "improved" or unimproved." Only in the group of adenitis cases is there a sufficient number to warrant any special attention.

It is obvious that in considering results we must regard both general and local changes. Criteria of improvement or unimprovement must therefore contemplate both subjective and objective deviation from the former state; must include (1) the patient's sense of illness or well-being, the fact of development or loss of anorexia, loss or increase in weight, change in the general appearance of the patient, and (2) locally, increase or decrease in area of disease (for instance, size, appearance of fluctuation, suppuration or sinus tract in lymph nodes), appearance or disappearance of tenderness, fluid, etc. (for instance, in the abdomen), change in amount or character of discharge from operative sites, the healing or nonhealing of granulating areas, gain or loss in arthritic function and change in tenderness or the degree of pain in such disease. It was on the basis of such criteria as these that the patients were finally classified as "improved" or "unimproved."

1: All Diagnoses: Of the 94 cases receiving treatment sufficient to justify classification as "improved" or "unimproved," 64 received ultraviolet and 30 (the controls) were under the glass screen. The percentage of "improved" in the treated cases was 54 and that of the control cases was 56, which means that the two groups of patients fared equally well. It must be remembered, however, that the control cases received the long ultraviolet rays and visible rays. And, before we can be certain of the effect of such rays, the latter should be separately screened out. Until this is done one is not justified in saying that such a group of cases as those we have constitutes an adequate control for the group of treated cases. The results in all cases are shown as follows:

Results—all cases

Total cases	94		
Treated	64		
Controls	30		
Treated		*Controls*	
Improved	35 = 54.5%	Improved	17 = 56.5%
Unimproved	29 = 45.5%	Unimproved	13 = 43.5%

2: Adenitis: Results in the group of adenitis cases are on the whole a little better than those for the total number treated, as the following tabulation will indicate:

Results—adenitis

Total cases	37		
Treated	28		
Controls	9		
Treated		*Controls*	
Improved	19 = 68%	Improved	5 = 55.5%
Unimproved	9 = 32%	Unimproved	4 = 44.5%

Certain individuals in this group showed such strikingly beneficial results as to properly rule out coincidence, and we have the feeling that, in a certain number of cases of tuberculous adenitis and in the average case of nonspecific cervical adenitis, ultraviolet light very frequently is of material benefit. It must be said, however, that there are many cases of this type of disease which do not yield at all to this therapy.

3: Pigmentation: It is well established that pigmentation is produced by the short ultraviolet rays, and that, when these are screened out,

tanning does not occur. For instance, prolonged and repeated exposure to sunlight through window glass will not lead to sunburn. Much has been made of the significance of pigmentation in heliotherapy, and considerable stock has been placed in its prognostic value. For instance, Rollier determines routinely the progress of those under treatment by the degree of pigmentation, and in his judgment those who fail to pigment usually do not do well. He ascribed a hypothetical capacity to the pigment by assuming that it transforms the longer rays into more effective but less penetrating short rays. He stated what is apparently a well-known fact that the longer rays penetrate skin, tissues, membranes, etc., more deeply than do the shorter rays. He also stated what is equally well known, that the shorter ultraviolet waves are therapeutically valuable while the worth of the longer rays is still quite unknown. He felt that pigment allows and even may facilitate the penetration of the long waves to the depths of the skin and then transform them into shorter waves. But this is purest theory and is without a single known supporting fact. Rollier has made a great and an important contribution to therapeutic medicine with his heliotherapy work, but he has not shown us that the rationale lies in the power of pigment to transform ultraviolet rays.

One may on rational grounds take the position that pigment probably has nothing to do, certainly in a favorable way, with the effect of light on the body. One may hold that pigment develops in the skin as a result of irritation, such as may be caused by sunshine, heat and kindred irritants. And if pigmentation is the result of irritation, may it not be thought of as a protective mechanism which tends to resist, throw off, or absorb the irritant? It is a fact sufficiently well known to be trite that the pigmented skin of the swimmer in the late summer can withstand with impunity many times the amount of sunshine which in early summer would lead to extensive sunburn.

It is comparatively easy to create and to regulate pigmentation by means of an ultraviolet lamp. When the initial dose is very short and below the duration necessary to cause an erythema, and when the duration of the treatments is gradually increased, very little discoloration of the skin appears, even though the final exposure may be an hour and the lamp be a comparatively short distance away. On the other hand, it is quite a simple matter to cause pigmentation with the lamp. A single erythema dose, or certainly a very few such doses, will lead to considerable tanning. In our cases we obtained very little pigmentation, and the

pigmented and nonpigmented patient improved or failed to improve irrespective of the discoloration of his skin. It is interesting in this connection that recently Woringer and Sala (4) have exposed one arm of patients to ultraviolet light until pigmentation was established. They then tested this and the normal arm with tuberculin and found much less reaction in the pigmented than in the normal arm. Conversely they found much more intense "takes" in the pigmented arm when they applied vaccine virus to both arms. At the instance of Dr. L. N. Gay in the Protein Clinic, we produced pigmentation on the right arm of ten people. These he tested on both arms simultaneously with several different pollen extracts and found no difference whatever in the response.

Although the skin of white and colored patients absorbs ultraviolet light at a different rate and degree there was no appreciable or decided difference in the eventual results in the two lots.

4: General Tonic Effect: There is one feature of the study that should come in for special mention, for it has been conspicuous throughout the work. It is the general sense of well-being which many patients, even many without improvement in local condition, experience after beginning light treatment. It happened that a very large majority of our patients became enthusiastic over the therapy for this reason. Many of them felt better and ate better and gained weight. One patient, a colored man of 21, with multiple tuberculous lesions of the bones and skin, gained 22 pounds in nine months and underwent considerable improvement. He was then placed under the screened lamp, when his sense of well-being became much less noticeable. He lost his appetite and some weight. Another patient, a white woman with a very small tuberculous cervical lymph node, showed the same reaction in marked degree. She and possibly ten others requested to be put back on the other lamp although not one of them knew what was the difference between the two lamps.

Was this response psychic? May not the patients have been boosted up by the idea that something active was being done for them? This would be one's first thought. But the fact is that patients put directly on the screened lamp experienced no tonic boost, no signal subjective improvement and no noticeable increase in weight. It is admitted that in several instances of this type the patients were convalescing from operation or illness and were patients in whom such a reaction would be expected. But the thing about it is that those under the screened lamp experienced not nearly so noticeable a response.

The study is by no means completed and should be continued for a long time with the employment of different screens and different sources of ultraviolet light.

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THE FATIGUE CONSCIENCE IN TUBERCULOSIS

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The treatment of the individual patient with pulmonary tuberculosis in an ambulant stage presents one of the most difficult problems in medical practice. In a sanatorium the physician has behind him the momentum of institutional routine and the impetus of mass psychology; patients respond readily to these influences with the necessary behavior. In severe and advanced cases the patient is in bed under the care of a nurse, and the physician can depend on his orders being carried out accurately. The ambulant patient in private practice, no matter how excellent his resolutions and how virtuous his intentions, is difficult to control. This classification includes the "suspected" case, the "early" case, the various types of low-grade cases, and the "arrested" case.

The treatment of tuberculosis is unlike that of, say, malaria, in which the patient only needs to take the medicine prescribed by the physician; or unlike that of appendicitis, in which the surgeon rolls up his sleeves and carries out with his own hands the steps necessary to the patient's recovery. In tuberculosis there is no specific drug to prescribe, nothing for the physician to do with his own hands. If the course of the disease is to be favorably affected, it can be accomplished only by means of radical changes in the patient's living habits persisting over long periods of time, and involving even his minor and intimate actions. Often the most trivial details in the patient's behavior will decide between success or failure in the treatment.

The task of the physician in these cases is to influence the patient to adopt such behavior and to persist in it. When this means the alteration of old and fixed habits, of mental attitudes and unconscious mechanisms, it is not easy of accomplishment. Merely telling the patient do this and don't do that is sadly inadequate. Deeply-founded human conduct cannot be revolutionized by admonition. Unless the patient possesses unusual determination and skill in self-discipline (not common accomplishments, as people go), he will fail in spite of his own

[1]Lincoln, Nebraska.

best intentions. A few words of instruction cannot change a life or a personality; nevertheless, just such a change is necessary if the treatment is to be successful.

Yet, the major portion of the fight against tuberculosis must be carried out on patients of just this type. Only a relatively small proportion of tuberculosis patients get to treatment institutions in time to effect the theoretical maximum of cure. The slogan of to-day is early recognition and early treatment. Perhaps we are already justified in looking forward to a day, with the mass of the medical profession trained in the methods of early recognition and early treatment, when an advanced case of tuberculosis will be as rare and as inexcusable as is a case of smallpox to-day.

To handle the ambulant case successfully, the methods of psychotherapy must be adopted. Men who are successful in treating this type of tuberculosis, whether they do it consciously or not, are practising psychotherapy. That art in this application is a new one, however, and its practice is not widespread. It still needs to be reduced to a standardized routine available to the busy general practitioner; and for this purpose it needs to be analyzed into clear-cut conceptions and well-defined methods.

The purpose of this paper is to define one such conception, for which the name *Fatigue Conscience* seems most appropriate. It will be found useful not only in tuberculosis, but in heart disease, and in any other conditions in which effort-economy is required. It consists of training the patient to acquire, by conscious effort, a new and lowered threshold to fatigue, which eventually ceases to depend on deliberate response to consciously recognized symptoms, and becomes an automatic habit.

We find in many cases of low-grade infection that, after the patient has been put on his rest-schedule and has kept quiet for some time, after his pulse and temperature have come down and his weight has increased, he will come to the physician and say, "I feel worse than I did before I started treatment. I am more tired and can stand less effort." His physical condition is in every way better, but he *feels* worse. That is because his sensations have become to some degree trained. It is not true that he is more fatigued than he was before. He merely recognizes fatigue now and admits it to his consciousness, which he previously refused to do.

The office-case of tuberculosis is frequently of the type that refuses to recognize and admit fatigue. The patient has diffuse lesions in the lungs, is 20 per cent below standard weight, with temperature and pulse around 100; yet he is ceaselessly and feverishly busy and active about

home or business affairs. He insists that he feels good; in fact he presses this information before it is asked for; he is constantly and restlessly on the move, and no one can make him stop (the thing that brought him to the physician's office was gastrointestinal symptoms, or headache, or frequent colds). It appears that his natural protective mechanism of fatigue-consciousness has been somehow shifted out of gear.

This state of affairs has two explanations. In the first place, this relatively excessive activity is not an efficient, well-directed expenditure of effort; it is much more of a distracted panic. It is quite analogous to the wobbling of a spinning top, which spun quietly and maintained a steady position as long as it had plenty of power; but, when its energy has run down, it can no longer remain steady, and begins to make an impressive show of activity. In the human body, genuine poise requires that energy be plentiful and well-balanced. For instance, the endocrine balance may be upset by a slight deficiency in a single gland and the resulting behavior might be exactly what has been described; similar conduct can be the result of an alteration of the equilibrium between the three nervous systems in the body, the central, the sympathetic, and the vago-cranio-sacral.

Second, this excessive activity is the result of an unconscious mental defense mechanism. The patient feels that he is losing out physically; he cannot stand as much work nor do as well in his play as he did before; he is not as good as other people. So he forces himself into a greater show of physical activity, just to show the world that he is all right. He makes himself do things and keep on doing them, just to prove that he can do so. This whole process may be below the level of conscious recognition. It usually is. But not always. Much traditional superstition still prevails in the different strata of our population, about "fighting off a sickness;" "not giving up to sickness;" "working off a fever;" "I won't go to bed or I'd have to stay there." The folk-belief is frequently found that, as long as one pretends that one is strong and active, one can keep on being so, and that thus in some way one is deceiving the disease and playing a trick on it.

We are gradually leaving behind us the age when the entire human tradition tended to refuse to recognize fatigue and indisposition, and to drive the human body at high pressure and without respite. Yankee "ambition," the "strenuous life," American "hustle" and "go-getting," the romantic Victorian ideal of staying up late and rising early and working *hard* and living on a crust of bread in a dark attic, represent a

waning conception of human heroism, which however has left behind it a vast amount of physical and psychic damage.

Man has evolved a mind for the purpose of coördinating the activities of various parts of his body and disregarding the minor and more immediate needs of its individual members, in order to subserve a loftier and more distant purpose. However, in our modern high-pressure civilization, this slavery of the body to the mind is frequently carried to the extreme, to the eventual danger of both body and mind. The body still has certain requirements that may not be neglected, no matter how lofty the mind's purpose.

Therefore, we are compelled to make use of the mind for the reverse of its original purpose: to concentrate attention on the needs of the body or of its individual members; to break up those ascetic inhibitions which would disregard the natural signs of fatigue. In this we deliberately train the mind to await these signals, to recognize the earliest degrees of them, and to indulge them, for the direct purpose of saving the body from disaster.

Merely to "prescribe rest," for an office-patient whom one sees once a week, gets nowhere. It is a vague gesture in the dark. Even to lay out a schedule of hours of rest and to define rest objectively may be inadequate. What rest is, and the amount of it required by an individual patient, is purely relative; it depends on a complex interaction between that individual's pathological process, his native capacity, and his environment. For some cases "rest" must be bed in a darkened, silenced room for many weeks. For other cases "rest" merely means an easier job.

In practice the amount and degree of rest required by any individual is determinable by his reaction to effort. Nature has endowed him with the faculty of recognizing the point at which he has reached an unfavorable limit in his capacity to exert, which will serve him usefully if he will but cultivate it. If he develops this ability to pay attention to the natural feelings of fatigue, he can readily, and better than the physician, ascertain his effort-limit, and remain within it. This is different from resting on a schedule; it may require months of training to learn, in which schedules and other things play their parts. Cases of compulsion-neurosis to activity may need to be put at complete rest in bed for a long enough period to break up their inhibitions and permit them to become relaxed; this may take from two weeks upward. Sedatives may be necessary to help get started. Some patients learn it fairly

well on a limited-effort schedule, such as being permitted to be up two hours at a time and then resting in bed for an hour between. The chief rôle of this formal preliminary rest period is to free them from the compulsion to activity and get them accustomed to resting. After this comes a period during which they are physically willing to rest, and the restriction of activity should continue as long as the physical inclination to rest persists.

This second or "lazy" stage frequently presents serious difficulties because of the patient's mental reactions. He will become alarmed because he has lost his former "pep" and energy; because he now no longer feels as active and ambitious as he did before the doctor got hold of him. He sees that he is not able to endure the amount of exertion that he thought he could endure before he began treatment. He remembers how, before he came under the physician's care, he was able to do as he pleased. Now he is physically unable to do so. That is more than he can understand. "So much rest is making me weak," he protests, and pleads for a restriction of diet to reduce his weight and a system of exercises to make him feel more active and vigorous again.

The treatment of this condition, which is largely a mental one, must be psychiatric in nature. The patient's mind must be influenced, by means fair or unfair. The following methods are suggested:

1: If the physician can gain the patient's absolute confidence, the patient will do much better in accepting the physician's arbitrary instructions and obeying them. This is accomplished by

a. Cultivating a pleasing personality and manner;

b. Evincing a personal interest in the patient;

c. Giving the patient the impression that one is thoroughly familiar with the subject;

d. Displaying real ability in handling the patient's minor troubles and problems.

2: To gain a patient's coöperation, it is necessary to gain his interest. This is achieved by explaining to the patient his malady and his situation so thoroughly that he has a vivid picture of it in his mind. He must be made to grasp clearly:

a. The general conception of the pathogenesis of tuberculosis;

b. The significance of exertion and fatigue;

Exertion in the normal person produces lactic acid in the muscles, causing the sensation of fatigue. The lactic acid is readily eliminated and the fatigue sensation disappears.

In the tuberculous patient exertion produces, in addition, the distribution of tuberculoprotein from the lesion. The patient thus has a double dose of poison. The tuberculoprotein is not easily nor quickly eliminated, and may set up a long train of trouble, even to reopening and spreading a healing lesion.

c. The cause and nature of his former apparent energy.

d. The reason for his present feeling of lethargy: he has now been enabled to recognize by means of his physical sensations how badly depleted his physical reserves really were.

e. The need of catering to the present feeling, which will involve the following explanations:

The healing of lesions by fibrosis;

The effect of excessive activity on a healing lesion;

The conception of the need of rest for mobilizing the systemic forces for defense and repair. (In an acute fever Nature puts the body at rest compulsorily; in low-grade, chronic states, her primitive impulses are "talked out of it" by his highly organized, high-pressure civilized mind.)

3: Warning will do more good with some than with others. In all cases it is well to point out the dangers and lay vivid stress on them.

a. Overactivity will lower the general systemic reserve; if the patient persists in it, he will eventually have to go to bed against his will, and by that time it will be a complete collapse. Then his prognosis will be worse.

b. The effect of overactivity on the lesion itself is to produce a hyperaemia about it, and carry tuberculotoxin all over the body, as well as to soften the lesion, with the resulting egress and spreading of bacilli to new foci.

4: Assurance and positive suggestion are after all the most direct and valuable of the methods of psychotherapy.

a. Keep a picture in the patient's mind of what he is accomplishing and can eventually accomplish by strict compliance with instructions;

b. Encourage him to look forward to future activities and pleasures as the reward of present patience and persistence;

c. Keep him posted on his progress; point out concretely each step forward that he has made and each point he has gained; and connect up these good results directly to his own commendable efforts. This makes him willing and eager to play the game.

In spite of my best efforts, I have lost patients at this stage to exercise-specialists and professors of reducing diets. Perhaps some of them got well nevertheless; it would be quite in keeping with the tricks that Life sometimes plays. But some of them have come back to me months later in a condition where no help was possible, and my signature on a death-certificate was the outcome. However, if the patient gets through this stage successfully, he will have completed an essential part of his education

and laid the necessary foundation for the development of his Fatigue Conscience. In favorable cases (and among the type that we speak of, the ambulant kind, which come to the office for their diagnosis, the percentage of favorable cases is high), the time will come when the patient may be up and about, increase his activity, and indulge in more or less exertion.

At first, of course, he must be under close supervision, and must account to the physician for all of his time from the standpoint of physical effort. The physician observes his condition closely and frequently. This period is the time to prepare and educate the patient for his future. The doctor is a teacher, and the treatment of tuberculosis is a training. The object of the training is to enable the patient to recognize the limits of stress in which he can safely indulge, and to remain within them. These are some of the principles that he must learn:

1: There are some complete and permanent recoveries. We have no means of knowing beforehand which ones they are going to be; we can be sure of them only after they have had many years of continuous good health.

Relapses are dangerous; they always signify an increase in the quantity of involved tissue.

Therefore, the only safe course lies in regarding every case as an arrest; in watching carefully to guard against recurrences. The patient must be on guard for many years; during the period of his treatment he may as well regard it as being for the rest of his life.

2: Tuberculosis is a handicap. The patient, even after arrest is satisfactory, does not have the capacity to endure stress that other people have. He cannot do as much as others can without paying dearly for it. If he wishes to be safe, he must learn his limit and stay within it. He must become reconciled to being less and doing less in the world than other people.

3: How shall he learn what his limit is? By overdoing and getting sick again? By reopening a lesion and spreading it over more territory? This is expensive, dangerous, and unnecessary.

Fatigue will tell the story. It begins to plead its case in a faint voice long before the limit of safety has been reached, and long before danger is serious. However, at first, its voice is faint indeed. It must be carefully listened for in order to be recognized early; for by the time it becomes loud and insistent it may be too late. The slightest signs of fatigue, a heaviness of the feet, an ache in the back, an indisposition to get out of a chair, in a person whose diagnosis has been established, are signals of the highest significance.

4: The patient must *act* on these signals. To recognize them is helpful only if he takes them as admonitions to get off his feet. They do not seem urgent; the earliest faint signal does not *compel* him to rest, as does acute fever or severe fatigue. It may be hard for him to believe that rest is actually such an urgent necessity.

That is where his mind comes in. He is not to wait for *feeling*, but to use his reason, and to *rest*. Deliberately and voluntarily, he must lie down and rest, even though he does not feel "tired enough," and even though it impresses him as being silly. The intelligence must take command; that is the price of safety.

In story books and sometimes in real life, a brave disregard of fatigue may be heroism. In a patient with a diagnosis of tuberculosis in his history, it is inexcusable foolhardiness.

5: After the patient once gets the idea of obeying Nature's safety signals of fatigue by resting, he must drill himself consciously and constantly in this response. Three distinct stages are observable in his progress, if he persists in the proper course: (a) after he has carried out the prescribed behavior and taken his rest on slight signs of fatigue, he begins to feel less foolish and self-conscious about it; (b) after a time it becomes easier for him to recognize the slight symptoms of fatigue, and it requires less mental struggle to compel himself to rest when they are perceived; (c) gradually even the conscious registration of the fatigue signs is eliminated. Once more, these slight symptoms are not perceptible. But the response to them is now automatic. The patient now limits his activity in conformity with the fatigue signals, and does not even think about it. It seems to be a mechanism quite analogous to that of Pavlov's conditioned reflex. The patient now has a *Fatigue Conscience.*

6: The ultimate result, that of acquiring an automatic Fatigue Conscience, can be hastened by conscious training in the physical side of personal efficiency. The patient can learn to live his life and do his work efficiently, which means to accomplish the results desired with the least possible expenditure of physical effort. Here, the commercial world, with its motion analysis and its standardized methods of performing tasks, can teach us a great deal. For, after the patient learns how, he can accomplish quite adequate amounts of work with but little fatigue. He can, in the long run, achieve about as much in the world as his friends who are in good health, because he has learned to eliminate nonessential exertion. He works without waste of energy, without false motions, without friction. Instinctively he feels what is too much, and unconsciously he avoids it.

By studying his tasks, analyzing the movements comprising them, and striving to arrange them so as to accomplish the maximum result with minimum expenditure of effort, he can hasten his progress enormously.

The further the patient develops this automatic response to fatigue sensation by rest, the more he can be freed from the arbitrary restrictions of the physician's schedule and left to himself. The progress will of course be gradual, but the physician should keep up with it, and encourage the patient by lifting formal rules one by one as the patient advances. When the Fatigue Conscience has been developed to a point where it functions satisfactorily, the patient may safely leave the physician's continued supervision. Until then, he is not safe to do this.

The Fatigue Conscience is an essential element in the treatment (or rather training) of the ambulant and convalescent case, and it is an indispensable part of the mental equipment with which a patient must be furnished as he leaves the doctor's care. Without it, he can never be certain of the permanence of his improvement. Low-grade clinical tuberculosis is fundamentally the result of excessive stress. Even after a complete cure has been effected, if there is a repetition of the conditions that caused the disease the first time, the same disease will occur in the same way, except for the fact that there will be a larger area of involved tissue.

A training such as the above necessarily proceeds slowly. Progress varies with different patients; some need fuller explanations or more frequent repetitions, more vivid illustrations and analogies, more stringent warnings, than others, before they understand and coöperate. But, in general, the brief outlines here given suggest material for step-by-step work with the patient by means of conferences for instruction, follow-up and observation, that will require from three months to two years.

A SURVEY OF PRIVATE PRACTICE IN TUBERCULOSIS IN A LARGE CITY[1]

JOHN B. HAWES, 2ND

It was what Kipling calls "my insatiable curiosity" which led me to make this investigation. In other words, I wished to know why patients consulted me, what they consulted me for, what was the chief thing that troubled them, how much they had found out from their family physicians, and the answers to numerous other questions. Therefore I prepared a series of questions which I filled out after seeing and talking with 500 consecutive patients.

The first question I asked was: How did the patient happen to come to me? The answer is shown in the following table:

1: How the patient came

		per cent
Referred by a physician	262	51.5
Came of their own accord	175	34.5
Sent by their employer	75	14.0

The next speaks for itself. What was the chief thing that brought them to see me? One would naturally say it was to find out what was the matter with them, but the following table shows there were various factors which caused them to consult a lung specialist:

2: Why the patients came

		per cent
Fear of having tuberculosis	216	42.5
For advice and treatment	141	27.5
To confirm a previous diagnosis of tuberculosis	88	17.0
Medicolegal cases	33	6.5
To settle a dispute as to diagnosis	20	3.5
For relief of symptoms	6	1.5
To determine ability to work	4	1.5

The next table roughly shows what these patients complained of. The size of the figures is due, of course, to the fact that many patients complained both of symptoms related to their lungs and of general consti-

[1] Presented at the annual meeting of the American Climatological and Clinical Association, Quebec, Canada, May 15, 1930.

tutional symptoms. But the table shows, much to my surprise, a large preponderance of patients who came because they had a cough. I rather expected to find it the other way round.

3: Chief complaints of these patients

			per cent
Referred chiefly to the lungs		520	64.5
Cough	202		
Sputum	146		
Blood	108		
Pain	64		
Chiefly constitutional		254	31.5
Loss of weight and strength	154		
Shortness of breath	68		
Fever	32		
No complaint		28	4.0

I then wished to see on what I based my own diagnosis. The results are clearly shown in the next table and need no comment.

4: Diagnosis of tuberculosis based chiefly on

		per cent
History and symptoms	228	60
Physical examination	77	20
Haemorrhage	49	13
X-ray	25	7

While I firmly believe that there should be an X-ray examination of the chest in every case of this kind, I had felt that the vast majority of such X-rays offered purely confirmatory evidence and were not absolutely essential. I was distinctly surprised in tabulating the results to see the large percentage of instances in which I considered the X-ray an essential factor in diagnosis.

5: The X-ray was

		per cent
Confirmatory	246	57.5
Essential	174	42.5

The next table shows how many of these patients came in to see me in the early stages, how many moderately advanced, and how many far advanced. I was surprised and rather pleased to see that 43 per cent reached me when in the early and favorable stages of the disease. The actual figures are shown in the table.

6: State of disease when seen by J. B. H.

		per cent
Early	114	43
Moderately advanced	109	41
Far advanced	41	16

Taking those patients who reached me in an advanced and unfavorable stage, I next tried to determine whether it was the doctor's fault or the patient's fault that they did not get good advice earlier. The figures show that it is about a fifty-fifty proposition.

7: If diagnosis made late whose fault was it?

		per cent
Patient's fault	25	50.2
Doctor's fault	23	49.8

Where it was evident that it was no fault of the physician but that the patient was to blame, again I endeavored to analyze as shown below:

8: If the patient's fault to what was it due?

		per cent
Ignorance	32	72.5
Lack of periodical examination	8	18.0
Fear	4	9.5

And similarly, where I believed that the doctor was to blame for not steering his patient on the proper path sufficiently early in the disease, I tried to find out the reasons for this, which to me were of distinct interest.

9: If the doctor's fault to what was it due?

		per cent
Hurry or carelessness	14	51
Not speaking plainly	12	45
Fear of offending the patient	1	4

A fairly large number of these patients in this series did not have tuberculosis. I was naturally interested, therefore, in finding out what I believed to be the true diagnosis. As shown in the following table, bronchitis leads the field with debility and fatigue a close second.

10: If not tuberculosis, what was the true diagnosis?

		per cent
Bronchitis	65	32.5
Debility, fatigue	56	28.0
Nerve strain, neurasthenia, etc.	24	12.0
Bad tonsils, etc.	23	12.0
Miscellaneous, such as: a. Pneumonoconiosis b. Malignant lymphoma c. Dry pleurisy d. Bronchopneumonia e. Weak heart, *et al.*	31	15.5

Finally I asked myself in each instance if I felt that the problem of each of the patients was satisfactorily solved, or whether the difficulties and the stage of the disease were such that a satisfactory outcome was impossible. Of course, in no way have I given end-results but have merely tried to size up whether the patient offered a problem which was capable or incapable of solution. Perhaps I have flattered myself but I am an optimist by nature. The last table shows the figures as I classified them.

11: Outcome of case

		per cent
Satisfactory	379	79
Unsatisfactory	97	21

There are no special conclusions to be drawn from this study but there are, none the less, various striking points well worthy of comment.

In the first place the fact that out of 500 private patients 48.5 per cent came to consult their physician, in this case, myself, either of their own accord, or because their employers sent them, and were not referred by any physician, shows very plainly that, at least as far as tuberculosis is concerned, the public has taken the bit in its teeth, as it were, and is running its own race.

And again, the answer to the next question, why patients came to see me, showing that 42.5 per cent came of their own accord because they were afraid lest they had tuberculosis, is striking, and, to me, encouraging evidence that our endeavors to educate the public in the early signs and symptoms of this disease have not been in vain. And that these signs and symptoms were fairly early ones is confirmed by the fact that 42 per cent of these patients came to me in what I call an early and at least a favorable stage of the disease.

Finally, it is perfectly evident that there are two chief factors preventing our patients from getting an early diagnosis of their disease and proper treatment. These are hurry and carelessness in examinations and history-taking, and failure to talk plainly to the patient and to use understandable English.

THE PULMONARY EFFECTS OF INTRATRACHEAL INJECTIONS OF OLD TUBERCULIN IN RABBITS[1,2]

With Special Reference to Roentgenographic Changes Following Haemoptysis

CHARLES R. AUSTRIAN AND HENRY STUART WILLIS

The helpfulness of the roentgenograph as an accessory to establish the presence, extent, character and localization of pathological changes of the lower respiratory tract is established. The correlation of clinical, roentgenographic, pathological and bacteriological data has demonstrated the significance of many of the deviations from the normal viewed in films of the lungs of phthisical individuals, but has not determined always the precise nature of many more or less evanescent alterations that are noted. This has been true particularly of the diffuse mottling or miliary seeding that may be seen in roentgenographs of the lungs made shortly after an haemoptysis has occurred.

Generally, the report that a patient has pulmonary miliary tuberculosis suggests that he has a serious malady with a grave prognosis. Yet, what observer of experience has not been agreeably surprised or embarrassed to note with the passing months progressive fading of such shadows, *pari passu* with or even antedating the clinical betterment of the individual?

Some have interpreted the small, scattered, ill-defined shadows as newly formed tubercles and have regarded their fading as evidences of healing. Others, who have accepted Amberson's views, have regarded them as the result of a perifocal allergic inflammation consequent upon the implantation of tubercle bacilli into a sensitized soil and considered their disappearance indicative of the absorption of an inflammatory exudate.

The proper answer to the problem is of more than academic interest, for upon it depends a more nearly accurate diagnosis and prognosis in individual instances.

[1] From the Kenneth Dows Fund for the Study of Tuberculosis, of the Johns Hopkins University and Hospital, Baltimore, Maryland.

[2] Read before the Johns Hopkins Medical Society, May 12, 1930.

Although doubtless in some cases these ill-defined shadows are due to spreading tubercles, indicated by their development, their subsequent coalescence, the evidences of consolidation or of excavation and the progressive course of the disease that may ensue, in other instances, in which complete restoration of a normal roentgenographic appearance is established, one of two inferences is possible. There may have been healing of tubercle analogous to that described in animals by Gardner or in patients by Amberson, or there may have been complete absorption of an inflammatory exudate that had been formed when reinfection of a sensitized tissue occurred.

To determine the facts, in 1926, Austrian and Willis (1) undertook experimentally to simulate the clinical conditions encountered when a phthisical individual has had an haemoptysis, and studied the roentgenographic and pathological changes produced in rabbits according to the following procedure: Healthy rabbits were subcutaneously infected with a strain of tubercle bacilli of bovine type (B1), grown from two to three weeks on Petroff's medium, and suspended in physiological salt solution. From time to time after the inoculation the chests of such animals were X-rayed. From the first, technical difficulties were encountered. Even when respiration was inhibited by holding a flask of ether before the nose, the films of infected rabbits failed sometimes to show evidences of pulmonary infiltration, although anatomical study showed gross lesions in the lungs. Inasmuch as it seemed possible that the vibration of the pulmonary tissue caused by the rapid action of the relatively large heart might be an interfering factor, cardiac standstill was brought about in addition to the induced apnoea. To bring about these two conditions synchronously, many procedures were tested; and, of them all, electrical stimulation of the vagus proved to be the best. An electrode was applied to the midcervical region over the carotid sheath; but even when this method was utilized the film usually indicated less disease than was demonstrable at necropsy. The most satisfactory films were obtained when the exposures were made for $\frac{3}{4}$ second, with a spark gap of 1 inch, at a distance of 24 inches, with a current of 5 milliamperes, using a double screen with film.

After pulmonary changes had developed as a result of the subcutaneous infection, in order to parallel the conditions that exist when an haemoptysis occurs clinically, blood was injected directly into the trachea of the animal. The blood used for injection was aspirated from the heart of a rabbit, and, in order to inhibit coagulation temporarily, it was

drawn into a syringe containing a solution of heparin, in the proportion of one milligram of heparin to each 20 cc. of blood.

In the series of experiments that were reported in 1926, the following procedures were performed:

1: Rabbits with pulmonary tuberculosis were injected intratracheally

a: With normal blood.

b: With blood to which a suspension of tubercle bacilli in physiological salt solution had been added. The bacillary suspensions were prepared as follows: The microörganisms in physiological salt solution were centrifugated, filtered through cotton, and diluted to contain from 7 to 12 bacilli to the oil-immersion field. One or one and one-half drops of this suspension from a 22-gauge needle were added to 1 cc. of blood.

c: With physiological salt solution to which were added tubercle bacilli in the same numbers as in the experiments in which blood was the menstruum.

2: Normal rabbits were treated in the same manner as the already tuberculous animals.

About eighty experiments were made.

The lungs of animals that received intratracheal injections were examined with the X-ray (1) before injection, (2) immediately thereafter, (3) on each of the succeeding 5 or 6 days, and (4) after periods of one to three weeks.

In none of the normal rabbits that were injected intratracheally with blood alone, or with suspensions of tubercle bacilli in salt solution or in blood, were acutely developing lesions demonstrable. In none of the normal rabbits, nor in any of the tuberculous rabbits that were injected intratracheally with blood alone, did changes develop that were comparable roentgenographically or anatomically to those found in some of the tuberculous rabbits that received intratracheal injections of suspensions of tubercle bacilli in blood. Tuberculous rabbits, injected intratracheally with tubercle bacilli in physiological salt solution, developed pulmonary foci identical with those that followed similar injections of tubercle bacilli suspended in blood.

SPECIMEN PROTOCOLS

The protocols of several experiments are illustrative.

Sanguineous Suspension of Tubercle Bacilli Injected into the Trachea of a Tuberculous Rabbit

Rabbit 22: May 5, 1925: Subcutaneous inoculation in the groin with bovine tubercle bacilli. *June 16, 1925:* Intratracheal injection, 2 cc.

normal blood. X-ray examination of the chest on the succeeding three days showed nothing abnormal.

June 23, 1925: Intratracheal injection, 3 cc. of blood with tubercle bacilli. The X-ray film of the chest, 24 hours after injection, showed a new shadow of increased density in the lower lobe of the left lung. The shadow was about 1 x 0.75 cm. in diameter and, although uniformly dense, had ill-defined margins that faded gradually into the density of the surrounding tissue. It was the type of shadow interpreted usually as evidence of a recently formed lesion.

Forty-eight hours after the second intratracheal injection, the animal was bled to death and autopsied. On the dorsal aspect of the left lung was an elevated area of consolidation, grayish brown, gelatinous, about 2 cm. in its longest diameter, and with irregular margins. Toward the cephalic end of this area, as well as just to the left of its caudal end, were several small, depressed, pigmented spots, of a deep orange or chocolate color. The cut-section, viewed with the unaided eye, showed the pleural border of this solidified area to be elevated above the general surface of the lung and its mass lacked the open, mesh-like appearance of the surrounding tissue.

Microscopically, the pleura over the involved lung did not present the irregular wavy outline seen over normal lung, but was smooth as if it were tense. In the densely consolidated parts, the predominating cells within the alveolar spaces resembled epithelial cells, but they were less ovoid as a result of compression. In the area of less dense consolidation more elongated cells, with eccentrically placed nuclei, filled half or more of the individual alveoli. Numerous polymorphonuclear leucocytes were seen throughout the exudate. Red corpuscles, though present, were less numerous than the color of the fresh specimen indicated they would be. Small accumulations of serum and of pigment were seen also. Throughout the area of exudation there were a few tubercle bacilli, singly or in small clumps, and generally intracellularly placed. The alveolar walls were slightly thickened and some of the capillaries were dilated.

Throughout the remainder of the lung tubercles were seen, an outer zone of lymphocytes surrounding groups of large epithelioid cells, and often a central zone of necrosis. The peripheral collar of lymphocytes was thicker than is seen usually, and contained a few polymorphonuclear leucocytes and cells resembling epithelioid cells, but the perifocal inflammation around these lesions was not striking.

The pathological changes that developed in the rabbits that were reinfected by intratracheal injection of tubercle bacilli were similar in all respects to those described by Bezançon and Serbonnes (2) in 1914.

Sanguineous Suspension of Tubercle Bacilli into the Trachea of a Normal Rabbit

Rabbit 71: Normal. *February 27, 1926:* Intratracheal injection, 3 cc. of blood with tubercle bacilli. *February 28, 1926*: Roentgenograph of the lungs showed no new shadows. *March 1, 1926:* The rabbit was bled to death from the femoral artery.

Examination: The dorsal and lateral surfaces of both lungs were mottled with large areas of discoloration, varying from a dark amber to chocolate. These were not sharply demarcated, the surface of them was not elevated, and none was dense or indurated.

Microscopic examination of sections of such discolored portions of the lungs showed that the reaction to the blood was comparatively widespread. Many alveoli contained red corpuscles or discolored serum, and in such areas there was atelectasis. The several small areas of bronchopneumonia that were seen were made up exclusively of small round cells, and no polymorphonuclear or epithelioid cells were found. A few tubercle bacilli were seen in the alveolar walls, usually intracellularly placed.

From these experiments it was concluded that the nature of the pulmonary lesions that develop acutely after reinfection of the tuberculous animal is clear. The rabbits were sensitized because they were already infected; the lesion was a rapidly developing exudation of cells and serum identical with that which appears characteristically whenever there are new implantations of tubercle bacilli in an animal already tuberculous; the exudate was absorbed spontaneously in several instances just as is the collateral inflammation that develops about small foci of tubercle bacilli experimentally introduced into an infected animal. Although the failure of noninfected animals to react similarly seemed to validate the conclusion that the changes described were due to allergy and not to the formation of tubercles or of localized areas of bronchopneumonia, such as those described by Meltzer and Auer, by Blake and by others when pyogenic cocci were introduced through the trachea, it seemed desirable to establish this datum beyond question.

During the past year, therefore, a series of experiments were carried

out that differed from the original ones only in that, instead of a suspension of living tubercle bacilli, an aqueous dilution of Old Tuberculin was injected into the trachea of tuberculous and of normal rabbits.

The protocols of two experiments are illustrative.

Aqueous Dilution of Old Tuberculin Injected into the Trachea of a Tuberculous Rabbit

Rabbit 6: May 22, 1929: Subcutaneous inoculation in the groin with 0.5 cc. of a heavy suspension of R1 five weeks old. *June 22, 1929:* Intratracheal injection, 2 cc. of 2.5 per cent Old Tuberculin containing a small amount of lamp-black. The roentgenograph of the chest, 24 hours after injection, was not satisfactory.

Forty-eight hours after the intratracheal injection, the animal was bled to death and autopsied. Examination showed two areas of gelatinous consolidation, each about 1 cm. in diameter, in the left lung, and another lesion of like size in the right lung. The gross section of the lungs showed several smaller foci of consolidation about the larger ones. The largest area beneath the pleura caused a bulging of that membrane.

Microscopically, over the areas referred to, the pleura was smooth and tense. Throughout the consolidated parenchyma, the outlines of the alveolar walls were difficult to define; the alveoli were filled with large, epithelial-like cells, numerous polymorphonuclear leucocytes with pigment in their cytoplasm and an occasional red corpuscle. The capillaries were dilated throughout the involved tissue.

Aqueous Dilution of Old Tuberculin Injected into the Trachea of a Normal Rabbit

Rabbit 11: Normal. *June 19, 1929:* Intratracheal injection, 1 cc. 2.5 per cent Old Tuberculin, to which a small amount of carbon was added to facilitate histological study. *June 22, 1929:* The animal was bled to death and autopsied.

The lungs were normal in appearance. In several of the normal animals, small areas of diffuse haemorrhagic discoloration were seen in the lungs, a study of which did not show the presence of consolidation.

Microscopically, in several small localized areas there was slight thickening of the alveolar walls, marked dilatation of the capillaries, a slight infiltration with polymorphonuclear leucocytes, many of which contained small particles of carbon, and numerous small round cells. A moderate grade of atelectasis was present also. Within the lumen of

some of the large bronchi, débris, leucocytes and red corpuscles were seen. It was evident that Old Tuberculin had a slightly but definitely irritative effect upon the normal tissues.

Whether or not this irritative effect was due to Old Tuberculin or to some of the products contained therein prompted us to do similar injections of aqueous dilution of watery extract, which was prepared by extracting pulverized tubercle bacilli with water at 54° for 48 hours, and then decanting after the mixture had stood in the ice-box for a week. This solution was put intratracheally into normal rabbits, in some animals in the strength of 2 per cent dilution, and in others in the strength of 50 per cent dilution. These animals were killed at two days and four days after the injection, and their lungs were examined histologically with the result that practically the same degree of irritation was noted as that found in the animals receiving Old Tuberculin.

DISCUSSION

The experimental data that have been presented demonstrate that when tubercle bacilli are introduced through the trachea into tuberculous lungs, focal areas of inflammation develop that are analogous to those represented in the pulmonary roentgenographs of tuberculous patients within a short time after an haemoptysis has occurred.

The prompt development of the exudative response, the character of the pathological changes and the absence of a like reaction in noninfected animals suggested that the changes described were due to a state of allergy and not to the formation of tubercles, a suggestion substantiated by the fact that identical changes resulted when tuberculin alone was injected through the trachea into tuberculous lungs.

These data indicate that although a number of hazy, ill-defined shadows seen in roentgenographs of the lungs may, in many instances, represent a seeding of those organs with fresh tubercles, in others, when the films have been made shortly after an haemoptysis has occurred, they may picture areas of exudation due to a specific allergic reaction of the lungs that have developed independently of the formation of new tubercles. Such a response of the tissue, though accompanied perhaps by a marked symptomatic reaction, may be evanescent, nonprogressive, and overcome with relatively little permanent local damage.

The shadows produced by the two types of response cannot be differentiated; therefore it is apparent that the roentgenographic appearance styled pulmonary miliary tuberculosis may not of necessity forecast a

progressively advancing disease and that the gloomy prognosis given generally, when it is observed, is not justified always. This fact is important, for it reëmphasizes the need of repeated correlations of clinical data with roentgenographic mutations throughout a period of time, to foretell more accurately the evolution and the outcome of pulmonary tuberculosis.

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THE LYMPHOCYTIC-MONOCYTIC RATIO IN EXPERIMENTAL TUBERCULOSIS IN GUINEA PIGS[1]

EDWARD B. BOSWORTH

In their study of the monocytic blood picture of animals inoculated with tubercle bacilli Cunningham, Sabin, Sugiyama and Kindwall (1) suggested that the ratio between the percentage of monocytes and the percentage of lymphocytes might have considerable prognostic value, since the monocytes tended to increase in numbers and the lymphocytes to decrease in direct ratio to the severity of the disease. This suggestion has found considerable support in clinical studies made on tuberculous patients by Morriss and Tan (2), Medlar (3), Flinn and Flinn (4), and in animal studies by Gardner (5). It is also suggested in older papers of Bender and DeWitt (6) and Hussey (7), as these authors showed an increase in monocytic cells and a decrease in lymphocytes in animals having a rapidly progressive tuberculous infection.

The present experiment has been undertaken to study the contrast in the lymphocytic and monocytic blood picture, as it is presented in two groups of guinea pigs inoculated respectively with virulent and with avirulent tubercle bacilli. Theoretically if the L/M Index can be accepted as giving an accurate indication of the individual's reaction to tuberculosis there should be a striking difference between that of the two groups. This was found to be the case in our experiment.

LITERATURE

Bender and DeWitt determined the normal blood count for guinea pigs. In cases of acute progressive tuberculosis they found either a terminal leucocytosis or leucopoenia with a progressive decrease in the lymphocytes, a preterminal increase in the endothelial cells and an absence of eosinophiles. In a study made on guinea pigs inoculated with the avirulent R1 tubercle bacillus Hussey found an increase in the circulating lymphocytes during the period of greatest reaction to the infection. In animals inoculated with H37, a virulent strain, the counts showed erratic variations, with the polymorphonuclear leucocytes greatly increased.

[1] From the Gaylord Farm Sanatorium, Wallingford, Connecticut.

Cunningham, Sabin, *et al.*, found the L/M Index to be lowered in rabbits having progressive tuberculosis. Gardner (4), working on guinea pigs, found an accelerated influx of monocytes when the tuberculous infection was becoming generalized and many new tubercles were in process of formation.

In a clinical study Morriss and Tan found in cases of active tuberculosis a lowered L/M Index due to a decrease in lymphocytes and a corresponding increase in monocytes. Although he does not grant the value of the L/M Index, Medlar found that there is an increase in circulating monocytes and a decrease in the lymphocytes, as well as an increase in the neutrophiles and total white count, in acute cases of tuberculosis. Flinn and Flinn suggest that an increased neutrophile/lymphocyte ratio and a decreased lymphocyte/monocyte ratio indicate a poor prognosis. Cunningham and Tompkins (8) found that the monocytes are practically always increased in number in tuberculosis. They found the monocyte/lymphocyte ratio, the inverse to that used in this paper, to parallel clinical severity in tuberculosis. The ratio is referred to as a useful mathematical expression for the extent of invasion compared to the resistance of the individual.

The supravital staining technique used in this experiment is described by Sabin in a study on living human blood cells (9).

METHODS

Ten guinea pigs were inoculated subcutaneously into the right groin with 0.2 cc. of a suspension of virulent tubercle bacilli, and 5 animals were similarly inoculated with avirulent microörganisms. The animals were of the same age and varied in weight from 486 to 685 gm. The temperature of the animal room was kept fairly constant. The experimental animals were fed regularly on grain and fresh vegetables.

The suspension of virulent bacilli designated as G9 was prepared from a fresh subculture of a strain of tubercle bacilli isolated from sputum in the Gaylord Farm Laboratory in 1927. It has been found in former experimental work to kill guinea pigs with the same dosage in about 65 days. The avirulent suspension was from a fresh subculture of R1 bacilli obtained from the Saranac Lake Laboratory. The suspension of virulent bacilli was diluted so that it averaged three bacilli per microscopic field; the R1 suspension was twice as strong.

No blood counts were made until four weeks after the inoculation. From then on counts of 200 cells were made weekly, using the supravital

technique of Sabin, on blood taken from a small ear-vein. The blood counts were made between 9 A.M. and 12 M., and the blood count on each animal was made at nearly the same time of day each week. The vital-staining technique was preferred because it gives a more informative picture of the monocytes and because there is less chance of confusing intermediate and large lymphocytes with monocytes.

The weight of each animal was recorded at the time of the blood count as well as at autopsy. Complete autopsy was made on each animal as it died and on one of the R1 group for comparison.

Blood counts were made and weights were recorded at weekly intervals on two normal guinea pigs as controls.

RESULTS

At the time of the first count each inoculated animal had an enlarged lymph node at the site of the inoculation. As the lymph nodes enlarged, those of the G9 group showed a much more rapid growth than those of the R1 group. In each case of the former group suppuration of the inguinal lymph nodes occurred before the animal died. In no case of the latter group did the lymph nodes break down. As the virulent infection progressed, superficial lymph nodes in the neck and axilla could be palpated. The controls and the R1 animals showed a constant increase in weight. The G9 group showed at first a slight gain with a subsequent loss of weight which became more rapid toward the end. These animals began to look and act definitely sick as they began to lose weight rapidly.

At autopsy of the G9 animals generalized tuberculous infection was shown by enlargement of practically all the lymph nodes. Suppuration of lymph nodes occurred only at the site of the inoculation, although caseation was found generally throughout the lymphatic system. In all cases the liver and spleen were enlarged and filled with tubercles and caseated areas. Tubercles and a greater or less amount of consolidation were found in the lungs of each of this group. In the animal which lived the longest (105 days) extensive honeycombed cavitation as well as a large amount of fibrous tissue was found in both lungs. In one case tubercles were found in the colon and in two cases in the epididymis. Autopsy of one of the R1 group, 104 days after the inoculation, showed only one lymph node at the point of injection which had caseated but which at the time of autopsy was apparently undergoing resorption.

Since this paper deals with the L/M Index which is calculated from the percentages of lymphocytes and monocytes rather than the total num-

ber, the total white count was not made at the time of each differential. The first counts made four weeks after inoculation showed a difference between the indices of the G9 and of the R1 group; the average R1 index was higher. This difference became more marked in the G9 animals which lived the longest. Chart 1 shows the percentage of lympho-

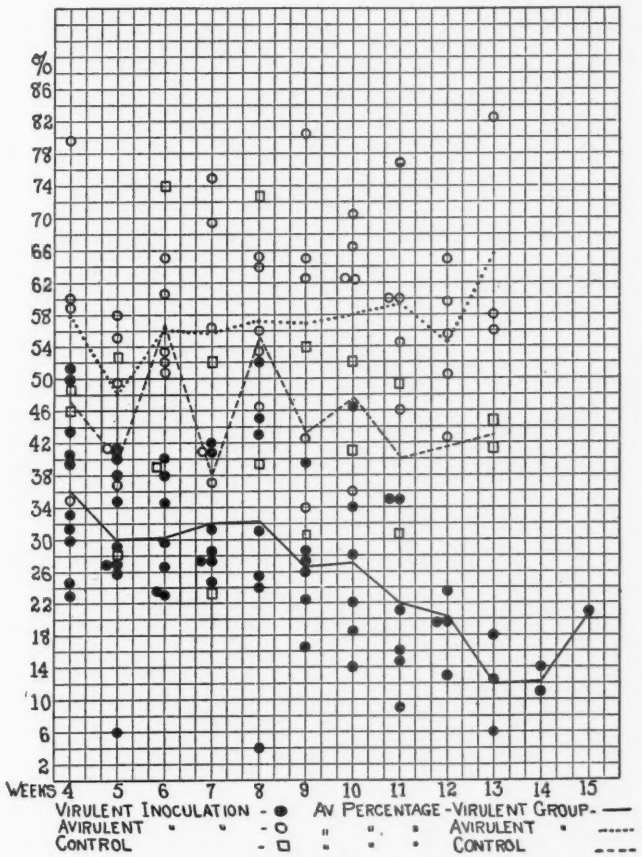

CHART 1. LYMPHOCYTIC PERCENTAGES

cytes at each count of all three groups, chart 2 gives the percentage of monocytes at each count, and chart 3 shows the resultant L/M Index. In all the charts the abscissa gives the time in weeks after the inoculation and the ordinate gives the percentage at the weekly count. In graphic presentation it is very clearly shown that, in the group having virulent microörganisms, the lymphocyte percentage is lower and the monocyte

percentage is higher than in the R1 or the control group. This difference is strikingly demonstrated in chart 3 of the L/M Index. In our counts on the control animals and the R1 group there seems to be no significant difference in the lymphocyte and monocyte percentage or in the indices

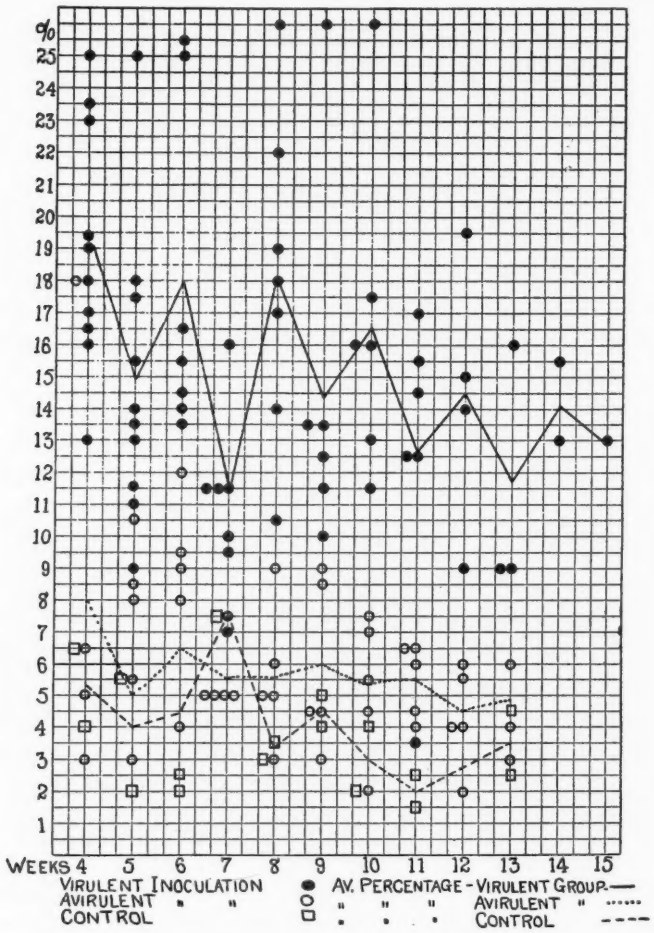

CHART 2. MONOCYTIC PERCENTAGES

of the two groups. In a few instances the percentage of lymphocytes in the G9 group is higher than some of the R1, and the percentage of monocytes in some of the R1 group was at times higher than that of some of the G9; but when the average of each group is computed and charted the difference is quite marked in the counts of each week.

The neutrophiles, in the earlier counts on the G9 group and in all the counts on the R1 and control animals, come within the normal limits of variation as found by Bender and DeWitt (6). Four of the former group showed a preterminal increase, but the other 6 came within normal range throughout the course of the infection.

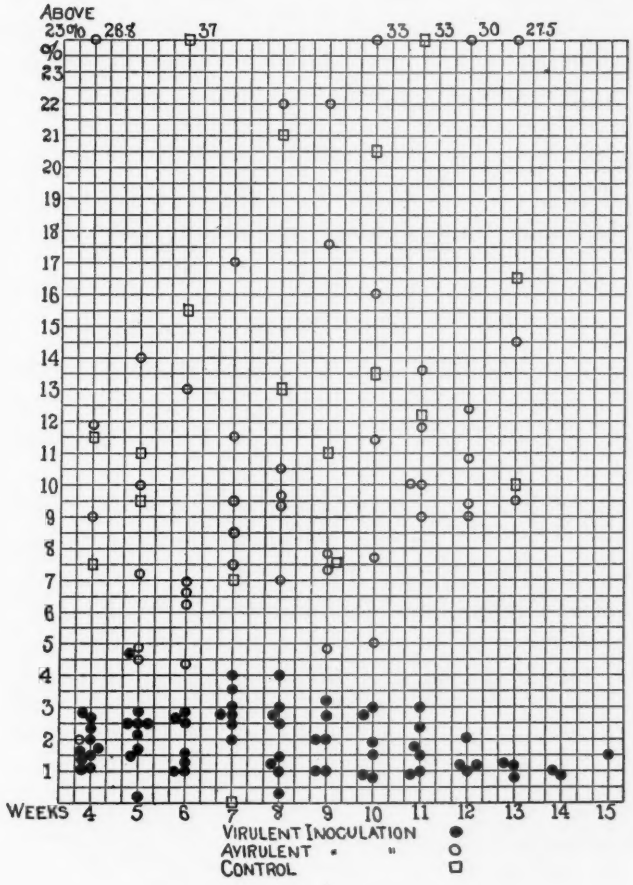

CHART 3. LYMPHOCYTIC/MONOCYTIC INDICES

In none of our animals was a marked eosinophilia and only a few Kurloff bodies were found.

DISCUSSION

The results of this study lend support to the theory, held by Sabin, Medlar, Morriss and Tan, Flinn and Flinn, and others, that the blood

picture is an important indication of the way in which the disease is progressing. When the lymphocytic and the monocytic percentages are correlated in the L/M Index the progress of the disease is more clearly shown than by total counts or by percentages alone. When the host is losing the fight against his infecting microörganism the index is found to be very low in spite of wide fluctuations in the total white counts. When, on the other hand, the host is able to overcome the attack of the tubercle bacillus, as in the case of the R1 infection, the index is high,—within the range of that of uninfected individuals. Or, in other words, a continued low index seems to be a strong indication of a losing fight and a poor prognosis. While in progressive tuberculosis in animals suppuration of lymph nodes and loss of weight show the course of the disease, the blood-picture changes occur before there are any visible effects on the animal.

CONCLUSIONS

1. Guinea pigs inoculated with a virulent strain of tubercle bacilli develop a blood picture characterized by a high percentage of monocytes and a low percentage of lymphocytes. The ratio between these percentages and the L/M Index is correspondingly low.

2. Guinea pigs inoculated with an avirulent strain of tubercle bacilli (R1) overcome the infection and present a blood picture but slightly different from uninfected animals and in striking contrast to that presented by animals dying of a virulent infection.

3. The L/M Index in experimental tuberculosis in guinea pigs is of value in determining the reaction of the animal to its infection.

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PLASMA PROTEIN, RED-CELL SEDIMENTATION AND SERUM LABILITY OF THE BLOOD IN TUBERCULOSIS[1]

L. R. JONES

The blood of many tuberculous individuals exhibits an increased sedimentability of the erythrocytes and an increased lability of the serum protein, and, although changes in these blood properties are not specifically related to tuberculous disease (the same phenomena may be observed in a variety of nontuberculous pathological states), they are used at the present time in connection with the diagnosis and prognosis of clinical tuberculosis. Irregular changes in the quantitative distribution of the plasma proteins incident to tuberculous infection have been noted by many observers.

This report deals with these properties as observed in the blood of 20 tuberculous and of 20 normal, male, human subjects. An attempt is made to compare these properties as observed in tuberculous and in normal subjects and also to correlate changes in erythrocytic sedimentability and serum precipitability with changes in the quantitative distribution of the various fractions of plasma protein occurring incident to tuberculous infection.

METHODS EMPLOYED

Blood specimens were collected from an arm-vein (without stasis) after a fasting period of 14 hours. A portion of the specimen was oxalated and centrifugated, the plasma was collected, and fractionation of the protein was promptly undertaken. Fibrin was separated by recalcifying diluted plasma and collected on a small glass rod. Globulin was coagulated with 1.5 molar concentration of sodium sulphate and removed by filtration, the nitrogen of the filtrate representing that contained in the albumin and nonprotein constituents. Nonprotein nitrogen was determined as contained in the tungstic-acid filtrate. The various fractions were quantitatively determined by calculation from the amount of nitrogen recovered after kjeldahl digestion.

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In determining the erythrocytic sedimentation-index, heparinized blood (0.5 mgm. heparin per cc. of blood) was placed in glass tubes of 4 mm. inside diameter containing a blood column 100 mm. in height. The tubes were set aside at room temperature for one hour, the corpuscular layer serving as a guide from which to record the descent (millimetres) of the cell column. Tubes were then centrifugated at 3000 R.P.M. to ensure complete sedimentation of cells and the cell-volume

TABLE 1

	CASE 20	CASE 12	CASE 3	CASE 19	CASE 6	CASE 5	CASE
Age in years	34	17	47	26	23	24	
Weight in pounds	175	130	140	129	125	125	1
Pulmonary tuberculosis (advanced)	Mod. A	Mod. A	Mod. A	Mod. B	Mod. B	Mod.	Mo
Plasma, 100 cc.							
Total protein in gm.	8.40	7.77	8.09	7.99	7.54	7.52	7.
Fibrin, gm.	0.39	0.46	0.44	0.41	0.41	0.41	0.
Globulin, gm.	2.59	2.93	3.54	2.96	2.27	3.02	3.
Albumin, gm.	5.42	4.38	4.11	4.61	4.86	4.09	3.
Protein quotient $\frac{\text{Alb.}}{\text{Glob.}}$	2.0	1.4	1.1	1.5	2.1	1.3	1.
Erythrocyte sedimentation, 1 hr.: mm.	18	20	44	13	28	51	39
Cell volume, per cent.	55	51	45	52	52	40	48
Sedimentation index	0.40	0.40	0.80	0.27	0.58	0.35	0.
Serum precipitation with aluminum sulphate:							
0.02 per cent.	−	−	−	−	−	−	−
0.03 per cent.	+	−	+	+	−	+	+
0.04 per cent.	++	−	++	++	++	++	+
0.05 per cent.	++++	+	++++	++++	++++	++	++
0.06 per cent.	++++	++	++++	++++	++++	++	++
0.07 per cent.	++++	++	++++	++++	++++	++	++
0.08 per cent.	++++	+++	++++	++++	++++	++	++
0.09 per cent.	++++	++++	++++	++++	++++	++	++
0.10 per cent	++++	++++	++++	++++	++++	++	++

recorded in millimetres. The sedimentation index was computed as the quotient of sedimentation (millimetres) occurring in 1 hour divided by sedimentation (millimetres) representing the possible maximum as determined by centrifugation. Since an anaemia *per se* may be an aetiological factor in a rapid sedimentation of erythrocytes, it is preferable to record the sedimentation rate in terms relative to the amount of possible (complete) sedimentation.

For the serum precipitation tests a portion of the blood specimen was

set aside for an hour and a half to permit clotting, after which the serum was separated by centrifugation and collected. Various amounts of aluminum sulphate (concentrations ranging from 0.02 to 0.12 per cent) contained in a unit volume of 1 cc. were added to 0.2 cc. of the blood-serum in small test-tubes. The serum and reagent were carefully mixed and set aside at room temperature for one and one-half hours prior to the reading. A heavy flocculent precipitate that settled out, leaving a clear

TABLE 1

ASE 6	[illegible]	CASE 18	CASE 17	CASE 14	CASE 13	CASE 9	CASE 16	CASE 4	CASE 11	CASE 15	CASE 7	CASE 8	CASE 2	CASE 10	CASE 1
23	24	33	98	40	27	56	38	34	40	34	47	44	25	30	25
125	25	113	98	105	129	110	150	140	130	105	140	101	106	120	115
Mod.	Mod.	Mod.	Mod.	Mod.	Mod.	Far A	Far A	Far A	Far B	Far B	Far B	Far C	Far C	Far C	Far C
B		C	C	C	C										
7.54	7.52	7.36	7.33	7.82	7.17	8.05	8.05	7.21	8.05	8.23	7.67	6.76	7.11	7.41	7.08
0.41	0.41	0.46	0.44	0.57	0.48	0.50	0.41	0.41	0.56	0.48	0.54	0.35	0.13	0.39	0.47
2.27	3.02	3.11	2.09	3.70	3.79	3.05	2.73	2.65	2.80	3.04	2.55	2.60	2.96	2.74	2.61
4.86	4.09	3.79	4.80	3.55	2.90	4.50	4.91	4.15	4.39	4.71	4.58	3.81	4.00	4.28	3.99
2.1	1.3	1.2	2.2	0.9	0.7	1.4	1.7	1.5	1.5	1.5	1.7	1.4	1.3	1.5	1.5
3	51	39	46	56	57	12	17	38	37	45	53	26	31	40	47
2	40	48	43	35	35	46	40	49	37	45	38	38	48	41	43
0.58	0.85	0.75	0.80	0.86	0.87	0.22	0.42	0.74	0.58	0.81	0.85	0.41	0.59	0.67	0.82
−	−	−	+	−	−	−	−	−	−	+	+	−	−	−	−
−	+	+	++	−	−	−	−	−	−	++	++	+	+	−	+
++	++	++	+++	+	−	++	++	++	+	++	++++	++	+++	++	+++
+++	++	+++	++++	++	++	++++	+++	++++	++	++++	++++	++++	+++	++++	+++
+++	++	++++	++++	++++	++++	++++	+++	++++	++++	++++	++++	++++	++++	++++	+++
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+++	++	++++	++++	++++	++++	++++	++++	++++	++++	++++	++++	++++	++++	++++	++++

supernatant fluid, was recorded as "++++" while a very small amount of flocculent precipitate was recorded as "+" reaction and precipitates intermediate in amount were recorded as "+++" and "++" reactions, according to the amount and density.

EXPERIMENTAL DATA

The results obtained upon examination of the blood in 20 cases of pulmonary tuberculosis are listed in table 1. The individual cases are

arranged according to the clinical diagnosis obtaining. Maximal, minimal and average values for these blood properties, as observed in this group of tuberculous subjects, and in a group of 20 normal subjects are given in table 2. Table 3 indicates by symbols any increase, decrease or absence of change noted in the blood of tuberculous individuals as based upon the limits established for these blood properties in the group of 20 normal subjects.

The tables reveal a significant trend of alteration in these blood properties incident to the tuberculous state, consisting of a marked increase in serum lability as indicated by precipitation occurring with lesser amounts of the flocculating reagent, increased sedimentability of the corpuscles and a quantitative shift in plasma protein toward the fibrin and globulin fractions.

DISCUSSION

The data indicate that the total protein content of the plasma is not greatly altered incident to tuberculous infection in the human subject, as in all of the cases studied the protein content of the plasma was within normal range. The various protein fractions deviate from normal limits markedly. Significant increases in fibrin were noted in 19 of the cases. Case 2, with a fibrin content of 0.13 gm., was one of far-advanced pulmonary tuberculosis with a complication of myocarditis, and the blood specimen studied was taken only shortly before the patient expired. In 7 cases there was observed an increase in the amount of globulin, the incidence of such increase indicating that it bears no relation to the extent or advancement of the tuberculous lesion. A diminution in the amount of albumin, as was observed in 7 of the cases, was coexistent with an increase in fibrin or globulin. Albumin content of the plasma of the remaining cases was within normal limits.

In general, the stimulus afforded the organism incident to tuberculous infection induces little if any change in the protein level of the plasma; however fibrin and globulin fractions in many instances exhibit a quantitative increase. Increases in the latter are always associated with increases in fibrin; however an increase in fibrin may be noted in the absence of an increase in globulin. Decrease in the amount of fibrin was observed only in case 2.

The sedimentation rate of the erythrocytes was found to be definitely accelerated in 19 of the cases. Case 9 exhibited a sedimentation index of 0.22, barely within the upper limit of the normal range; the blood

TABLE 2

	20 NORMAL INDIVIDUALS			20 TUBERCULOUS INDIVIDUALS		
	Maximum	Minimum	Average	Maximum	Minimum	Average
Age in years	31	20	23	56	17	33
Weight in pounds	210	130	158	175	98	124
Plasma, 100 cc.:						
Total protein, gm.	8.42	5.86	6.95	8.40	6.76	7.63
Fibrin, gm.	0.31	0.18	0.26	0.57	0.13	0.43
Globulin, gm.	2.96	1.05	2.05	3.79	2.09	2.88
Albumin, gm.	6.10	4.12	4.64	5.42	2.90	4.29
Protein quotient $\frac{\text{Alb.}}{\text{Glob.}}$	5.20	1.50	2.39	2.20	0.76	1.47
Erythrocyte sedimentation, 1 hr. mm.	13.0	2.0	6.0	56.0	12.0	35.9
Cell volume, per cent.	61.0	43.0	52.0	55.0	35.0	44.0
Sedimentation index	0.26	0.04	0.12	0.87	0.22	0.63
	(NORMAL INDIVIDUALS)			(TUBERCULOUS INDIVIDUALS)		
Incidence of minimal precipitation with aluminum sulphate:						
0.02 per cent	0			4		
0.03 per cent	0			7		
0.04 per cent	0			7		
0.05 per cent	0			2		
0.06 per cent	6					
0.07 per cent	7					
0.08 per cent	2					
0.09 per cent	5					

TABLE 3

Blood of tuberculous compared with blood of normal individuals

	PULMONARY TUBERCULOSIS MODERATELY ADVANCED										PULMONARY TUBERCULOSIS FAR ADVANCED									
	"A"			"B"			"C"				"A"			"B"			"C"			
Case number	3	20	12	5	6	19	13	14	17	18	9	16	4	11	7	15	2	10	1	8
Plasma:																				
Total protein	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Fibrin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+
Globulin	+	0	0	+	0	0	+	+	0	+	+	0	0	0	0	+	0	0	0	0
Albumin	0	0	0	−	0	0	−	−	0	−	0	0	0	0	0	0	−	0	−	−
Sedimentation index	+	+	+	+	+	+	+	+	+	+	0	+	+	+	+	+	+	+	+	+
Serum precipitability with aluminum sulphate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

− = decreased.
0 = within normal range.
+ = increased.

specimen was taken only a few days prior to discharge as an "arrested" case. Active tuberculosis is usually associated with an accelerated sedimentation rate of the erythrocytes; however, the extent of acceleration is apparently not correlated with the patient's resistance, area of involvement, pyrexia, progressiveness of the lesion and such other factors as are reflected in the clinical diagnosis (table 1).

The minimal amount of aluminum sulphate yielding a precipitate constitutes an index of serum lability. Since normal sera gave minimal reactions within a range of 0.06 to 0.09 per cent concentration, in the event a concentration of less than 0.06 per cent yields a precipitate under these conditions, it may be interpreted as meaning an increased lability of the serum protein. The range in concentration (minimal) of aluminum sulphate yielding flocculation of the sera of tuberculous subjects was found to be from 0.02 to 0.05 per cent concentration of the reagent.

Increase in serum lability was noted in all of the tuberculosis cases studied, extent of increase bearing little or no relation to the type and extent of tuberculous involvement.

Lability of serum protein was not to be correlated with the distribution of globulin and albumin occurring in the plasma. Serum and plasma may not be entirely analogous with respect to content of globulin and albumin; however, by experiment it may be shown that the ratio of these fractions in the former is not at great variance with that obtaining in the latter. The average value (1.47) of the plasma-protein quotient observed in the tuberculous group was much lower than that observed (2.39) in the normal group; however, the plasma of many normal and tuberculous subjects with similar values for the protein-quotient exhibit dissimilar precipitabilities. Only in 9 of the 20 cases exhibiting increased lability of serum protein was there observed a decreased value of the plasma protein-quotient. Accordingly it seems probable that the latter property is related to changes in serum other than the ratio of albumin to globulin.

A fundamental point of interest in this investigation was the determination of the relationship existing between the distribution of plasma proteins and the sedimentability of erythrocytes. The data indicate that in the tuberculous individual there is a frequent association of an increased sedimentation index with an increase in plasma fibrinogen and only in some instances an associated increase in plasma globulin. This relationship of a hyperinosis to an acceleration in the sedimentation rate of erythrocytes was observed in 18 of the 19 cases exhibiting the lat-

ter property. In only one case, no. 2, was there noted an increase in sedimentability of red blood cells without increase in plasma fibrinogen, and the reverse relationship was noted only in case 9. Decrease in the amount of albumin was observed in 7 of the specimens studied, an increase in this moiety not being observed in any of the cases. A decrease in the ratio of albumin to globulin, as reflected in a decreased value of the protein quotient, was observed in 9 individuals of the series; however, a decrease in the value of the protein quotient appears to bear no definite relations to sedimentability of the blood corpuscles.

The conclusion, that an increase in fibrinogen or in globulin may be the causative factor *per se* in an acceleration of the sedimentation rate of erythrocytes, is not warranted, since it is possible that plasma-protein changes and the acceleration in the sedimentation rate may result from a common stimulating agency and yet be independent phenomena (1). In this study it was noted that blood specimens, as obtained from similar cases and exhibiting similar concentrations of plasma protein and protein fractions (cases 19 and 5, 16 and 4), may exhibit quite dissimilar sedimentation indices.

SUMMARY

In a comparison of the amount of plasma protein and of the fractions, fibrin, globulin and albumin, obtaining in 20 cases of pulmonary tuberculosis, with values for these properties in 20 normal subjects it was observed that the amount of plasma protein was within normal limits in all of the tuberculous cases. Fibrin was increased in 19 cases, and of these globulin was increased in seven. Albumin was within normal limits in 13 and decreased in 7 cases.

In the tuberculous group the average value of the protein quotient was 1.47 and in the normal group 2.39. In the former group 11 cases exhibited a value for the protein quotient within normal limits.

Quantitative shift in distribution of plasma protein in the tuberculous individual did not bear relationship to the type and extent of tuberculous involvement.

Marked increase in the sedimentability of the blood was noted in 19 cases of tuberculosis. Amount of increase however bore no consistent relation to the extent of tuberculous involvement or advancement of disease.

Increased precipitability of serum protein, as observed in all of the

tuberculous cases, could not be correlated with the various clinical diagnoses.

In 18 of the tuberculous individuals increased sedimentability of the erythrocytes was coexistent with an increase in plasma fibrinogen. In one case, no. 9, an increase in fibrinogen was associated with a normal sedimentation rate and in case 2 a decrease in the amount of fibrinogen was associated with an acceleration in the sedimentation rate.

Serum precipitability, though markedly increased in all of the tuberculosis cases, was not correlated with the ratio of albumin to globulin in the plasma.

The author acknowledges indebtedness to the staff of Mt. St. Rose Sanitarium for their coöperation in this study.

REFERENCE

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Correction

In the paper by Cunningham and Tompkins, *The Epithelioid Cell*, January issue, vol. xxiii, pp. 70–75, the following correction should be made: On page 75 the source of the *Reference* of paper by Morgan, now reading *Jour. Clin. Invest. (In press.)*, should read *Tr. Assoc. Amer. Phys., 1930, xlv, 67.*

EXPERIMENTAL JOINT TUBERCULOSIS

I. AN ATTEMPT TO PRODUCE LOCALIZED LESIONS IN GUINEA PIGS[1]

WILLIAM J. SPRING[2]

Experimental investigations of therapeutic problems in tuberculosis have suffered from two chief difficulties. It has been impossible to keep an experimental infection localized. And the wide variations occurring in untreated controls have made conclusions of doubtful statistical validity.

A general infection with a virulent organism is clearly not a fair test for any of the therapeutic measures now available because it would require a phenomenal curative agent to save the animal's life. If the bacillus is of lower virulence, there still remains the difficulty of finding an adequate measure of advancement of the infection, during life or at autopsy. In any case a generalized infection is not comparable to curable cases of human tuberculosis, in which active disease is limited to a few sites, however widely the bacilli may be distributed.

The variance in the course of infections produced under apparently identical conditions is known in every laboratory. As a result, conclusions drawn from small series are open to the objection that the differences encountered may be due to chance. With enough animals it is possible to avoid this objection by the use of statistical measures of variability. There still remains the objection that real differences may be submerged by chance variation. The more nearly the process can be standardized, the more sensitive will be the method.

The attempt was made therefore to produce a localized tuberculous infection under conditions as nearly standard as possible. The joint was chosen because it was thought that the course of the disease could be followed to some extent during life by means of clinical symptoms and by X-ray pictures.

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REVIEW OF THE LITERATURE

The earliest attempts to produce bone or joint tuberculosis consisted in trying to localize a general infection by means of trauma. Schüller (1) (2) inoculated dogs and rabbits by trachea or vein with tuberculous sputum or pieces of lung, at the same time producing luxations of several joints. Many of the injured joints developed changes which he thought to be tuberculous, although in the absence of microscopic examinations one cannot be certain. Krause (3), by a somewhat similar method, obtained tuberculous changes in about one-third of the injured joints, but in only one uninjured one. Salvia (4) reported somewhat similar results. Lannelongue and Achard (5), Friedrich (6) (7), and Honsell (8) were unable to confirm the localizing influence of trauma. Petroff (9) failed to produce localization in the limb by nerve section or vein ligation.

It is interesting that multiple caseous joint tuberculosis occasionally occurs spontaneously in rabbits with generalized tuberculosis, if the infecting organism is of relatively low virulence. Such a result was described by Courmont and Dor (10) with an attenuated bacillus of unknown type, by Cadiot, Gilbert and Roger (11) and Cobbett (12) with avian tubercle bacilli, and by Petroff (13) with the *BCG* bacillus. Occasional bone and joint foci occurring spontaneously in animals with generalized infection have been described also by Friedrich (6) (7), Honsell (8), and Fraser (14).

In 1886 Müller (15) injected tuberculous pus or sputum into the tibial nutrient artery in goats. There resulted in several cases chronic tuberculous foci in the tibia, sometimes with extension to the adjacent joints, but without generalization. Only a few of the animals developed generalized tuberculosis. Cheyne (16) repeated these experiments, using bacillary emulsions instead, but all the animals showing bone lesions had visceral tuberculosis as well. Müller (15) and Fraser (14) infected rabbits by way of the femoral artery, producing occasional bone foci, with generalization in every case. Somewhat similar results were produced by Friedlaender (17) by injecting tubercle bacilli mixed with lycopodium powder into the femoral arteries of goats.

The first worker to infect the marrow cavity directly was Cheyne (18), who injected human tubercle bacilli or sputum through brad-awl holes into the tibias of rabbits and guinea pigs. There developed extensive tuberculous osteomyelitis with extension into the joints in some cases. The animals were not observed long enough to determine whether the process would generalize. Fraser (14) produced marrow lesions in four out of seven guinea pigs. The fact that two rabbits, infected at the metaphysis, showed no lesions led him to ascribe a special immunity to the type of marrow found there. This was not confirmed by Ely (19). Allison and Fisher (20) produced similar lesions in dogs. The early microscopic changes after marrow infection in guinea pigs and rabbits are described in detail by Oliver (21). In none of the animals

infected by this route did generalization fail to occur if the animals were followed long enough.

Krause (3), Cheyne (18), Pawlowsky (22), Fraser (14), and Allison and Fisher (20) injected tubercle bacilli or tuberculous sputum into the knee joints of rabbits, guinea pigs and dogs. All injections produced tuberculous synovitis, in some cases with bone destruction. With the exception of two rabbits injected with human bacilli by Fraser, all the animals developed generalized tuberculosis if observed over twenty-two days. These two are said to have had chronic synovitis. The lesions are not described. Cheyne (16) succeeded in producing chronic tuberculosis of the wrist without generalization in a goat by injecting bacilli into the joint. The animal had received bacilli into the tibial nutrient artery at the same time, but showed no disease in the tibia.

The method of producing joint lesions by local trauma after general infection is obviously not suited to the purposes of this experiment. Infection by way of the arteries was not chosen, because by this method the location of the lesion is left too much to chance, preventing standardization. Direct infection of the bone-marrow was excluded because here also technical necessities introduce too many variable factors. There remained the direct injection of bacilli into the joint.

The fact, that in almost all animals reported to have been infected by this route generalization resulted, made it seem wise to seek an additional factor favoring localization. The extensive literature on allergy,which there would be little point in reviewing here, made it seem likely that a previous infection with bacilli of low virulence would have this effect. Such a procedure was favored also by the fact that in human joint disease the occurrences must be somewhat analogous. The direct introduction of bacilli into the joint of a human being not elsewhere tuberculous must be exceedingly rare. Human joint tuberculosis is a secondary infection.

EXPERIMENTAL

For the sensitizing infection the R1, a very avirulent strain of tubercle bacillus of human type, was chosen. Since for the second injection the right microörganism and dosage likely to produce the desired sort of lesion could not be predicted, it was decided to begin by trying several dosage levels of each of three organisms varying widely in virulence. All were of human type; the H37 the most virulent, the H305 the next, and the R1 the least.

For the purpose of standardizing the dose the counting chamber method of Jennings (23) was used, in slightly modified form.

The optical system described by the author was replaced by the actual dark field with a 1.9 mm. oil-immersion objective, with funnel stop. The inconvenience of using oil on the cover-glass as well as beneath the chamber is well repaid by the increased visibility. The bacilli stand out clearly and there is rarely doubt as to the nature of an individual object. Between 200 and 300 bacilli can easily be counted with little eye strain.

It was found that if, as described, the whole suspension was passed through the filter twice, almost all the bacilli were removed. This was obviated by filtering the suspension only once, with the exception of the first half cubic centimetre, more or less, which was returned to the funnel. In this way suspensions containing as many as 40,000,000 bacilli per cc. can be obtained.

When 200 bacilli were counted, it was found that all suspensions, even those with only a few hundred thousand bacilli per cc., contained clumps, but with a little practice it was possible to obtain suspensions the clumps of which were rare and never contained more than four bacilli. Since, with the optical system used, it is easily possible to count the individual bacilli in such clumps, their presence is insignificant if the dose injected is not less than 100 organisms. If larger clumps were found, the suspension was discarded.

The Petroff-Hausser bacterial counting chamber must be filled exactly; otherwise currents are set up which make accurate counts impossible. Even with a well-cooled lighting system the chamber dries out quickly enough to cause currents within a few minutes after filling. Consequently the counting must be done rapidly.

Owing to the high magnification it is necessary to use the fine adjustment continually so as to see those bacilli which do not settle upon the ruled surface. In all cases the chamber was filled at least twice. After calculation the suspension was diluted to the desired strength with M/15 Na_2HPO_4.

Under sterile precautions 49 male guinea pigs, weighing between 334 and 570 gm., all of which had negative reactions following the intracutaneous injection of 5 per cent Old Tuberculin received subcutaneously in the right groin 400,000 R1 bacilli, suspended in 0.5 cc. of M/15 Na_2HPO_4. All bacilli used in these experiments were grown between two and three weeks on a liquid synthetic asparagin medium. On the 28th day following this injection the animals were again tested with tuberculin. All were found to react positively.

Controls

Sixteen animals received no further injections. The outcome of the infections in this group may be seen in table 1. It will be noted that extensive visceral tuberculosis, due to the R1, was rare.

The remainder of the animals received into the left knee joint injections of tubercle bacilli, performed as follows:

The animal is fastened to a special board, which holds the lower limbs fixed in extension. The knee is depilated by plucking. The tip of a fine needle on a tuberculin syringe is then inserted through the skin into the patellar tendon, half-way between its tibial insertion and the lower end of the patella. The tip of the needle is then elevated, lifting the patella from the femur, and is caused to penetrate into the space so formed. The method was checked many times with diluted india-ink in dead guinea pigs.

Experiments with H37

On the 38th day following the injection of R1 sixteen guinea pigs, weighing between 332 and 565 gm., received H37 suspended in 0.1 cc. M/15 Na_2HPO_4. Four groups, of four guinea pigs each, received respectively 100,000, 10,000, 1,000 and 100 organisms.

The animals were examined clinically at intervals until they died or were killed. Then the joints were exposed and opened by a vertical slit along the outer edge of the patella. The greater part of the muscles was dissected away, the femur and the leg bones broken with bone forceps, and the whole joint put in a solution of 10 per cent nitric acid and 9 per cent formalin. After decalcification the joint was cut sagittally. One-half was saved for a gross specimen and the other trimmed for microscopic section. The degree of enlargement of the inguinal, retroperitoneal and bronchial lymph nodes, as well as the degree of macroscopic tuberculosis of the spleen, liver and lungs, were recorded as one, two or three plus. Smears of any exudate found were examined for acid-fast bacilli.

Clinical Course

Immediately after the injection a few of the animals limped but this disappeared within fifteen minutes in every case. Two hours later all which had received 100,000 bacilli limped definitely, but had no swelling. One of the animals receiving 10,000 (no. 5) appeared to favor the injected limb a little. This could not be confirmed a half-hour later. No other guinea pig showed evidence of reaction at this time. The next day all the guinea pigs in the first two groups showed a definite limp and swelling. One animal, receiving 1,000 (no. 11), showed a questionable limp, and of those receiving 100 one (no. 26) showed a doubtful swelling

and one (no. 25) a slight limp. Almost all, even in the first two groups, were free from symptoms on the third day, after which all the injected animals appeared normal. The symptoms described are thought to have been similar to a tuberculin reaction, in which the dosage would be expected materially to influence the severity.

After an interval of 18 to 40 days, all the animals again developed a limp and swelling of varying degree. With the larger doses the interval tended to be shorter, while with the smaller doses it was not only longer but more variable. Despite the delay there were no significant differences, correlated with dosage, in the average severity of symptoms eventually attained, or in the final outcome, though here again there was greater variation within the groups receiving the smaller doses.

X-ray photographs, taken on the 27th and 79th days following the injection, showed no bone lesions, even though considerable detail of bony structure could be distinguished.

Autopsy Findings

In each group two animals died spontaneously and two were killed with chloroform at the end of six months. The degree of visceral tuberculosis can be seen in table 1. It will be noted that, with two exceptions, all animals developed extensive disease.

In the knees no significant differences were found between the dosage groups, either grossly or microscopically, though there were wide differences between individuals. The commonest gross finding was an enlargement of the injected joint, with a partial obliteration of the normal depressions. This, though rarely absent, was often insufficient to be seen before removal of the skin. Sometimes there was a slight excess of fluid, usually clear, though more often none was noted. In most cases the enlargement was due to a thickening of the synovia. Usually this was yellow or bright orange in color, with an irregular surface. The orange color was present in every case but one and could often be seen outside the capsule, coloring the joint diffusely. In some cases the injected joint showed a mild hyperaemia of the capsule. Definite erosion of the cartilage was seen in only four cases and was slight in these. With the exception of a few minute, round, soft, gray areas seen in the marrow in six animals, no changes were found in the bones. There were no sinuses or pus.

Microscopic Findings

There were wide individual differences, which could not be correlated with dosage or with duration. In one case (no. 17) the synovial lining appeared perfectly normal. In another (no. 6) its only abnormality was a slight excess of lymphocytes and mononuclear cells. The latter varied considerably in different animals. In six (nos. 2, 5, 6, 8, 26, 29) the predominant cell was a mature fixed-tissue cell with an elongated small dark nucleus. Cells with larger pale oval nuclei, but still firmly fixed among collagen fibres, predominated in five (nos. 1, 4, 23, 25, 28). True epithelioid cells occurred in nine (nos. 2, 4, 7, 8, 11, 12, 23, 25, 29) and predominated in three animals (nos. 7, 11, 12). These three showed occasional typical giant cells.

Almost all the injected knees showed masses of fibrin on the synovial surface. In most cases these masses were invaded by mononuclear cells and were partially or completely organized. This resulted sometimes in papillae and often in extensive granulation tissue, occasionally with large hyaline necrotic areas (nos. 1, 19). In most cases (nos. 1, 11, 12, 19, 25, 28, 29) the granulations were easily recognized as tuberculous, but in some (nos. 2, 23, 26) not.

The subsynovial areolar tissue was oedematous in five (nos. 11, 17, 23, 25, 26) and showed some degree of lymphocytic infiltration in all but two (nos. 7, 30). This was very dense in twelve (nos. 1, 2, 5, 6, 11, 12, 17, 19, 23, 26, 28, 29). The infiltration was diffuse, but in most cases there were round nodules in which it was more dense than elsewhere (nos. 4, 6, 17, 19, 23, 26, 28, 29). Some of these showed central necrosis (nos. 17, 19, 26, 28, 29) without typical epithelioid cells. The latter were found diffusely in the subserosa in considerable numbers in six animals (nos. 1, 7, 11, 12, 23, 29) and formed characteristic tubercles in six (nos. 1, 5, 7, 11, 12, 26), in the last four of which typical giant cells were found.

The changes found in the subsynovial connective tissue extended in almost every case into the quadriceps muscles, where there was often extensive necrosis. The periosteum of the femur or tibia was also involved in almost every case. Definite erosion of the cartilage was found microscopically in only one (no. 12). The uninjected knees without exception showed a normal synovia.

Bone-marrow changes, while present in all but two (nos. 9, 15) of the injected legs, were nowhere severe enough to cause much bone destruction.

TABLE 1

Autopsy findings. Degree of enlargement of lymph nodes and extent of visceral tuberculosis recorded on an arbitrary scale.

NUMBER OF ANIMAL	FIRST INFECTION		SECOND INFECTION			SURVIVAL AFTER LAST INJECTION	CAUSE OF DEATH	MACROSCOPIC TUBERCULOSIS						
	Micro-organism	Dose	Interval	Micro-organism	Dose			Left inguinal lymph node	Right inguinal lymph node	Retroperitoneal lymph node	Bronchial lymph node	Spleen	Liver	Lungs
			days			*days*								
77	R1	400,000	–	–	–	13	Fracture					0	0	0
58	R1	400,000	–	–	–	17	Pneumonia	0	0	+		0	+	0
16	R1	400,000	–	–	–	24	Pneumonia	0	0	0		0	0	0
62	R1	400,000	–	–	–	24	Pneumonia	+	+	0		0	0	0
53	R1	400,000	–	–	–	25	Pneumonia	+	+	0	0	0	0	0
10	R1	400,000	–	–	–	31	Pneumonia	+	+*	+		+		0
66	R1	400,000	–	–	–	32	Undetermined		+	0		0	0	0
72	R1	400,000	–	–	–	39	Pneumonia		+	+		0	0	0
37	R1	400,000	–	–	–	49	Undetermined	0	+++*	+	0	0	0	0
76	R1	400,000	–	–	–	107	Tuberculosis	+++	+++*	+++		+++	++	+
70	R1	400,000	–	–	–	257	Tuberculosis?	++	++	0	++	0	++†	0
69	R1	400,000	–	–	–	501	Chloroform	+++	+++	++	+	+†	0†	+†
56	R1	400,000	–	–	–	502	Chloroform	+	+	+	+	0†	0	+†
55	R1	400,000	–	–	–	502	Chloroform	+	+	0	+	0†	0†	0†
59	R1	400,000	–	–	–	502	Chloroform	+	++	+	+	0†	0	+†
60	R1	400,000	–	–	–	502	Chloroform	+	+	+	+	0†	0†	0†
17	R1	400,000	38	H37	100,000	116	Tuberculosis	++	++	0		+++*	+++	+++*
1	R1	400,000	38	H37	100,000	171	Tuberculosis	+++	+++			+++	+++	+++*
2	R1	400,000	38	H37	100,000	180	Chloroform	++	+			++	++	+++*
4	R1	400,000	38	H37	100,000	180	Chloroform	+++	0			+++	++	++
5	R1	400,000	38	H37	10,000	150	Tuberculosis	++	++	++		+++	+++	++*
6	R1	400,000	38	H37	10,000	167	Tuberculosis	++	++			+++*	+	++*
7	R1	400,000	38	H37	10,000	180	Chloroform	+++	++		+++	++	+	+++*
8	R1	400,000	38	H37	10,000	180	Chloroform	0	+			++	++	+++

19	R1	400,000	38	H37	1,000	78	Pneumonia	+	0			0	0	+
23	R1	400,000	38	H37	1,000	176	Tuberculosis	++	++			+++	++	++*
11	R1	400,000	38	H37	1,000	180	Chloroform	++	++			++	0	++*
12	R1	400,000	38	H37	1,000	180	Chloroform	+++	+++			++	+	++
26	R1	400,000	38	H37	100	123	Tuberculosis	+	++	0		++*	+	+++
29	R1	400,000	38	H37	100	161	Tuberculosis	++	++	+++		+++*	++	++*
25	R1	400,000	38	H37	100	179	Chloroform	0	0			0	0	0
28	R1	400,000	38	H37	100	179	Chloroform	++	0	0		+++	++	++
34	R1	400,000	101	H305	100,000	118	Undetermined	+	++	0	0	+	0	0
33	R1	400,000	101	H305	100,000	130	Paratyphoid	++	++	++	++	+	0	0
6	R1	400,000	101	H305	100,000	210	Chloroform	++	0	++	+	+++	+++	+++
39	R1	400,000	101	H305	100,000	210	Chloroform	++	++	++	++	0	0	++
43	R1	400,000	101	H305	10,000	61	Undetermined	+	++	0	0	0	0	0
38	R1	400,000	101	H305	10,000	210	Chloroform	++	+++	++	+	0	+	++
44	R1	400,000	101	H305	10,000	210	Chloroform	+	++	++	+	0	++	0
64	R1	400,000	101	H305	1,000	91	Volvulus	+	+	0		0	0	0
54	R1	400,000	101	H305	1,000	136	Undetermined	++	+++	++	++	++	0	0
57	R1	400,000	101	H305	1,000	136	Undetermined	+	+	0	++	0	0	0
48	R1	400,000	101	H305	1,000	210	Chloroform	0	++	++	0	+	0	0
67	R1	400,000	145	R1	500,000	21	Ulcers	0	0	+		0	0	0
61	R1	400,000	145	R1	500,000	73	Ulcers	+	+	0	0	0	+	0
65	R1	400,000	145	R1	500,000	175	Chloroform	++	+	++	++	0†	++	0
73	R1	400,000	145	R1	100,000	72	Ulcers	+	+++	++		0†	0	0
71	R1	400,000	145	R1	100,000	100	Paratyphoid	++	++	0	++	0	0	0†
74	R1	400,000	145	R1	100,000	175	Chloroform	++	+++	0	+	0†	+	0

* Acid-fast bacilli found in smear.

† Microscopic section made to verify diagnosis.

All these lesions consisted of collections of epithelioid cells, often (nos. 5, 6, 7, 11, 12, 17, 23, 26) with typical giant cells. Hyaline necrosis existed in one or more foci in ten animals (nos. 1, 4, 5, 6, 11, 17, 23, 26, 28, 29), but was never extensive. While lymphocytes were present in most of the lesions, polymorphonuclears were rare except in the presence of necrosis.

Tubercles were found in all three bones, the epiphyses of the femur and tibia containing about three times as many as the shafts. That some, at least, of these lesions were haematogenous was indicated by the fact that in ten animals (nos. 1, 5, 6, 8, 12, 17, 23, 26, 28, 29) lesions of similar character were found in the bones of the uninjected legs. On this side the distribution between shafts and epiphyses was about equal. In four (nos. 4, 23, 26, 29) of the injected legs, marrow lesions were found continuous through small cortical openings with similar lesions outside the bone. Whether these represented extension inward or outward is uncertain. One of these lay near the tibial attachment of a cruciate ligament, where, in the guinea pig, there is normally a cortical defect, furnishing an ideal site for extension of the infection.

Experiments with H305

On the 101st day following the R1 inoculation, eleven guinea pigs, weighing between 494 and 750 gm., received 0.1 cc. of a suspension of tubercle bacilli, strain H305, into the left knee joint. Four animals received 100,000 organisms, three 10,000, and four 1,000.

The following day all the animals receiving the largest dose showed a marked limp and swelling. These symptoms disappeared completely between the third and the sixth day. In the second group only one animal (no. 38) showed such severe symptoms, though the other two did show swelling without limp. Of the guinea pigs which received the smallest dose, one (no. 64) had moderate swelling without limp for one day, the others remaining apparently normal. These symptoms are quite comparable, dose for dose, with those shown by the animals receiving H37.

The later clinical course was quite irregular. Five of the animals (nos. 34, 43, 64, 54, 57) never developed further joint symptoms. Three (nos. 33, 39, 48) never showed palpable swelling, though they did limp occasionally. Two (nos. 38, 44) showed occasional slight swelling, but were apparently normal when killed. Only one animal (no. 36) had

symptoms, a moderate limp and marked swelling, just before death. A comparison with the table will show that the above grouping does not correspond to the dosage groups.

Autopsy Findings

The macroscopic findings in the lymph nodes and viscera may be seen in table 1. The animals whose cause of death is given as undetermined probably died of paratyphoid fever, since there was an epidemic in the laboratory at the time. In these individuals the microörganism was not identified.

It is clear that the degree of visceral tuberculosis was much less in these animals than in those injected with H37. Yet the disease was present in most and quite extensive in one.

The gross changes in the injected knees were identical in kind with those of the H37 animals, but somewhat less in degree. In only two cases (nos. 36, 39) were they sufficient to cause appreciable enlargement of the joint. The commonest change was a thickening and orange discoloration of the synovia. Visible marrow tubercles occurred in one (no. 36) and excess of fluid in five (nos. 33, 36, 44, 54, 48). One (no. 43) looked perfectly normal in the gross.

The microscopic synovial changes were indistinguishable from those of the H37 group, except that the involvement of the subsynovial areolar tissue was, on the average, less extensive.

Five of the sections (nos. 33, 36, 39, 44, 54) showed places where portions of the joint cartilage were replaced by granulation tissue containing epithelioid cells. Four of these lesions (nos. 36, 39, 44, 54) were so placed that it seems probable they followed injury with the needle at the time of injection.

The bone-marrow was involved in four (nos. 36, 39, 44, 54) of the injected knees. The lesions were collections of epithelioid cells, sometimes (nos. 36, 54) with giant cells. Most of the lesions lay in the femoral or tibial epiphyses or in the patella and were often near openings in the cortex, either normal ones near the insertions of the cruciate ligaments (nos. 36, 39, 44), or pathological ones beneath eroded cartilage (nos. 36, 54) or periosteum (no. 36). Only one animal (no. 36) had extensive marrow lesions. This guinea pig was also the only one which showed marrow lesions on the uninjected side, or extensive visceral tuberculosis.

Experiments with R1

On the 145th day following the sensitizing infection, six guinea pigs, weighing between 560 and 740 gm., were given 0.1 cc. of a suspension of living R1 bacilli in M/15 Na_2HPO_4 into the left knee joint. Three received 500,000 and three 100,000 microörganisms.

The next day all six animals showed a marked limp and swelling, which soon subsided, so that no animals showed symptoms after the third day. None of the guinea pigs receiving the smaller dose showed any further symptoms. Of the other group one (no. 61) had a questionable swelling on the 43rd day, and another (no. 65) had a slight limp on the 85th day. No other joint symptoms were shown and all animals were symptom-free before death.

The macroscopic visceral findings may be seen in table 1. Three of the animals died of a disease of unknown cause, characterized by multiple cutaneous ulcers with crusts, and with small subcutaneous ecchymoses. One died of paratyphoid and two were killed. Extensive visceral tuberculosis was found in none.

The gross abnormalities in the knee joint were very slight. The injected knees were apparently normal in two (nos. 61, 73). One (no. 67) showed only a slight hyperaemia of the serosa. Three showed thickening and irregularity of the synovia. The bones appeared normal in all.

Microscopically the changes were still less severe than in the H305 group. In four animals (nos. 61, 65, 71, 73) considerable portions of the synovia were normal, though in all there was some degree of infiltration with lymphocytes and mononuclear cells. In five (nos. 65, 67, 71, 73, 74) there were small masses of fibrin, more or less organized, on the surface of the serosa. Epithelioid-cell collections occurred in the subserosal connective tissue in three (nos. 65, 71, 73), once (no. 65) with several giant cells.

The cartilages and ligaments and the quadriceps muscles were not involved in any animal. This was true also of the bones, with the exception of several minute necrotic lesions occurring in the bone-marrows of both legs of animal no. 71. These did not contain mononuclear cells and it is highly unlikely that they were tuberculous.

SUMMARY

Three types of human tubercle bacilli, of varying virulence, were injected, in varying measured doses, into the knee joints of guinea pigs,

previously sensitized by infection with a tubercle bacillus of low virulence.

Tuberculous lesions of the synovia, and in some cases of the bone-marrow, were produced, the severity of the lesions apparently depending more on the virulence of the microörganism than on the dose within the range examined.

The organism virulent enough regularly to produce joint lesions of appreciable severity usually caused severe visceral tuberculosis.

In view of the wide individual variations between animals treated alike, the lesions produced are of no use for therapeutic experiments.

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EXPERIMENTAL JOINT TUBERCULOSIS

II. COMPARATIVE EFFECTS OF TUBERCULOUS INFECTION IN NORMAL AND PREVIOUSLY INFECTED GUINEA PIGS[1]

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Since Koch (1) discovered that the tuberculous guinea pig reacts to the subcutaneous injection of tubercle bacilli differently from the normal animal, the literature on the subject of reinfection has become very extensive, and is too well known to require review here. There is general agreement that the immediate inflammatory reaction is more severe in the tuberculous than in the normal animal, but that the dissemination of infection is retarded, unless the reinfecting dose is so large that the immediate reaction kills the animal.

When it was found during the course of experiments described in a previous paper (2) that the immunity resulting from a previous inoculation with nonvirulent tubercle bacilli was insufficient to localize a secondary joint infection, it was decided to determine whether the differences between first infection and reinfection seen elsewhere hold true also in the joint. The literature of experimental bone and joint tuberculosis has already been reviewed in the paper referred to.

EXPERIMENTAL

Seventy-seven guinea pigs, weighing between 236 and 360 gm., reacted negatively to an intracutaneous injection of 5 per cent Old Tuberculin. Thirty-five animals, intended for reinfection, then received subcutaneously in the right groin 400,000 tubercle bacilli, of human type and of low virulence, strain R1, grown between two and three weeks on a liquid synthetic asparagin medium. The organisms were suspended in M/15 Na_2HPO_4, and counted in the Petroff-Hausser counting chamber by the method of Jennings (3), somewhat modified (2). About one month later these animals reacted positively to a repeated tuberculin test. For the infection of the knee joints the H305, a somewhat more virulent

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strain, also of human type, was used. These bacilli were grown and counted in the same way as were the R1. One million organisms, suspended in 0.1 cc. M/15 Na_2HPO_4, were injected under sterile precautions into the left knee joint. The schedule of injections is given in table 1.

The clinical symptoms were observed at intervals, and the limp and swelling recorded on an arbitrary scale as absent, one, two or three plus. Some animals died spontaneously, but most were killed. On the death of the animals the joints were exposed, the bones broken with

TABLE 1

Dates of injection of tubercle bacilli

GROUP	NUMBER OF ANIMALS	DATE OF R1 INJECTION	DATE OF H305 INJECTION	INTERVAL BETWEEN INJECTIONS
				days
TI	12	5/6/29	6/11/29	36
NI	12	None	6/11/29	—
TIIa	4	9/17/29	10/23/29	36
NIIa	4	None	10/23/29	—
TIIb	4	9/17/29	11/26/29	70
NIIb	4	None	11/26/29	—
TIIc	7	9/17/29	12/ 3/29	77
NIIc	6	None	12/ 3/29	—
NIII	8	None	1/ 7/30	—
TIV	8	1/16/30	2/21/30	36
NIV	8	None	2/21/30	—

All injections made on any one day were made with the same suspension.

bone forceps, and the joints removed and immersed in a solution of 10 per cent nitric acid and 9 per cent formalin. After decalcification the joints were bisected sagittally, one half preserved as a gross specimen, and the other half trimmed for microscopic section. In twenty-one reinfected and twenty previously normal animals the inguinal, retroperitoneal and bronchial lymph nodes, and the viscera were examined, and the degree of macroscopic involvement recorded on an arbitrary scale as zero, one, two, or three plus.

Clinical Symptoms

All the data regarding limp are recorded in figures 1 and 3, and those concerning swelling in figures 2 and 4. In these each column contains

all the data obtained from all the groups at a particular time-interval after the knee infection. The upper half of each chart refers to the previously tuberculous animals, and the lower half to those of first infection. Each animal examined at a particular time is represented by a dot placed in the row indicating the degree of limp or swelling shown at that time. The total number of dots varies in different columns because the intervals at which the different groups were examined varied. The curves connect the average heights of all the dots at each time-interval. Figures 1 and 2 represent the findings during the first two days, on a scale of hours. Figures 3 and 4 record the data for the first 81 days, by days.

One is impressed at once by the fact that the animals did not react quantitatively alike, that at most time-intervals the distribution of dots on the scale is very wide. This means that at a particular time one could not have told, in most cases, by examining a single animal whether it was one of first or of second infection. Yet the two groups showed definite differences in the course of the infection, which appeared quite clearly in every individual animal.

During the first few hours after the inoculation both groups showed a gradually increasing limp and swelling. At eleven hours the difference between them began to appear, the limp and swelling increasing in the tuberculous and decreasing in the previously normal animals. At twenty-four hours the symptoms were about at the maximum in the former, and had disappeared in most of the latter group. Some degree of immediate reaction was shown by every previously normal animal examined during the first 12 hours, though there were wide variations in severity. During the next few days the symptoms disappeared also in the reinfected animals. While there was an immediate reaction in both groups, it was, as one would expect, much greater both in severity and in duration in the previously infected group.

After a short period in which both groups were symptom-free, limp and swelling began to reappear. In the reinfected animals this recrudescence was gradual and occurred at first in only a few animals. In the animals of first injection the symptoms were far more severe and of more rapid onset. Of the 19 previously normal animals examined at this time, all developed a three-plus limp at least once, and 14 showed a three-plus swelling. In only one was the maximum swelling one plus. The suddenness of onset was greater than would appear from figures 3 and 4. In more than half the cases the maxima, both of limp and of

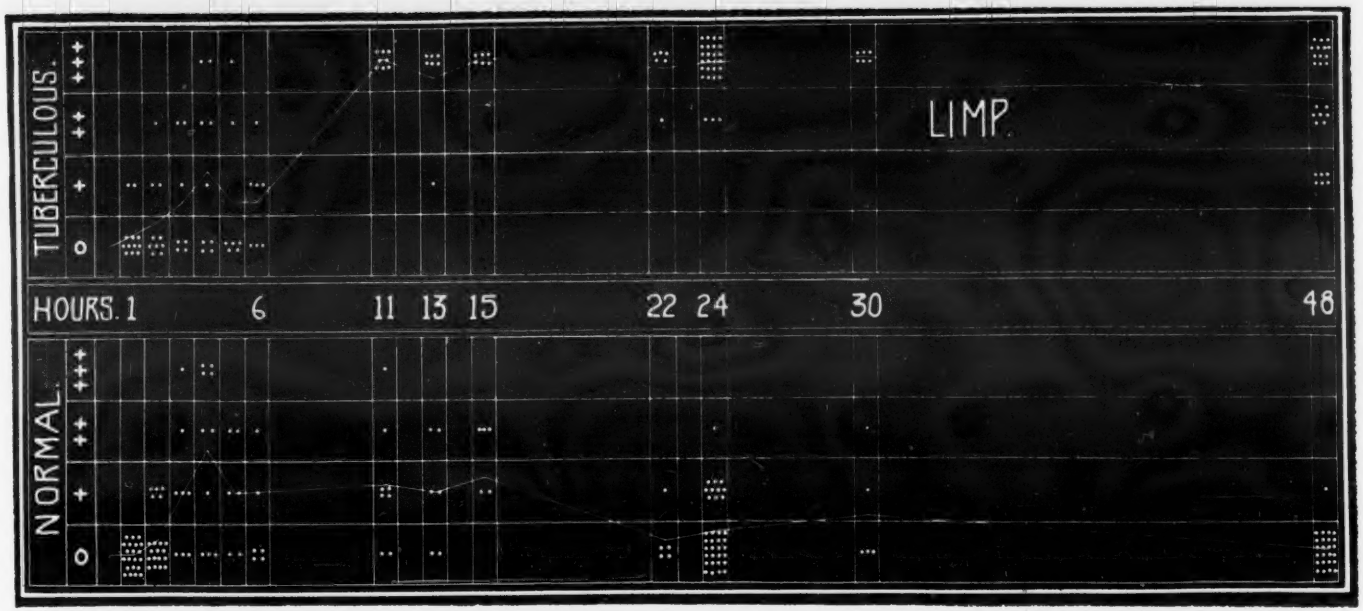

FIG. 1. DEGREE OF LIMP DURING 48 HOURS AFTER THE INJECTION OF TUBERCLE BACILLI INTO THE KNEES OF TUBERCULOUS AND OF NORMAL GUINEA PIGS

Each dot represents one animal observed at the time indicated by the column in which it appears. The degree of limp (on an arbitrary scale) is shown by the horizontal row in which the dot is placed. The average heights of the dots in each column are connected by a curve.

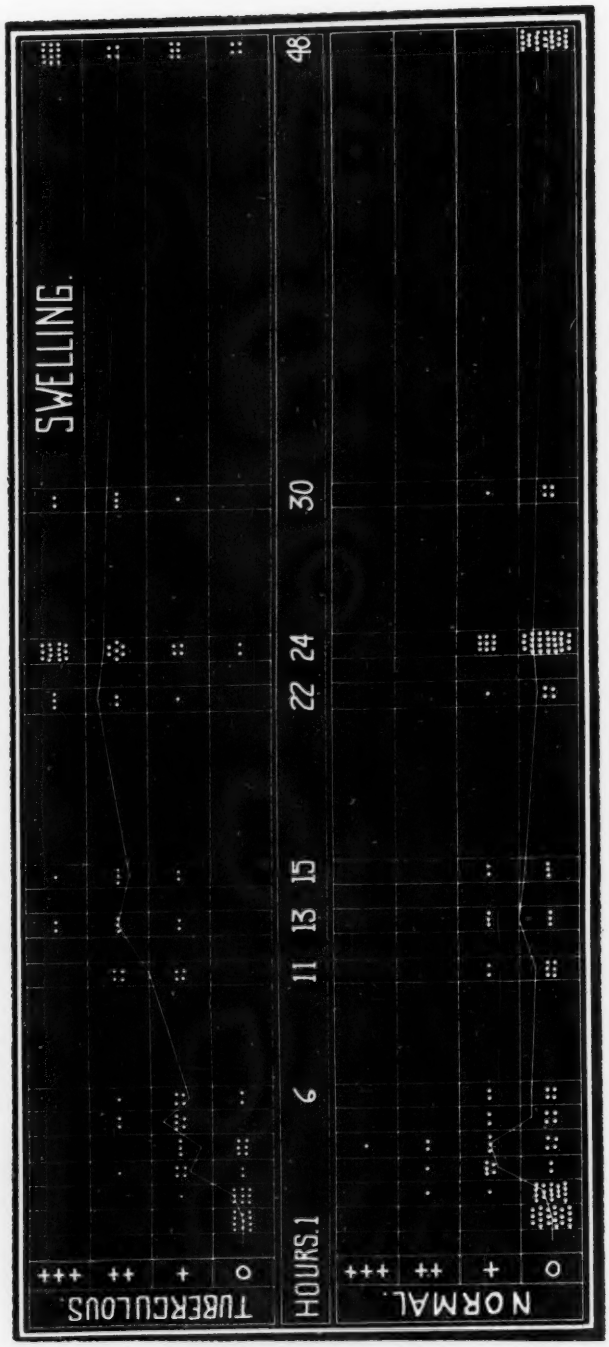

FIG. 2. DEGREE OF SWELLING DURING FIRST 48 HOURS RECORDED AS IN FIG. 1

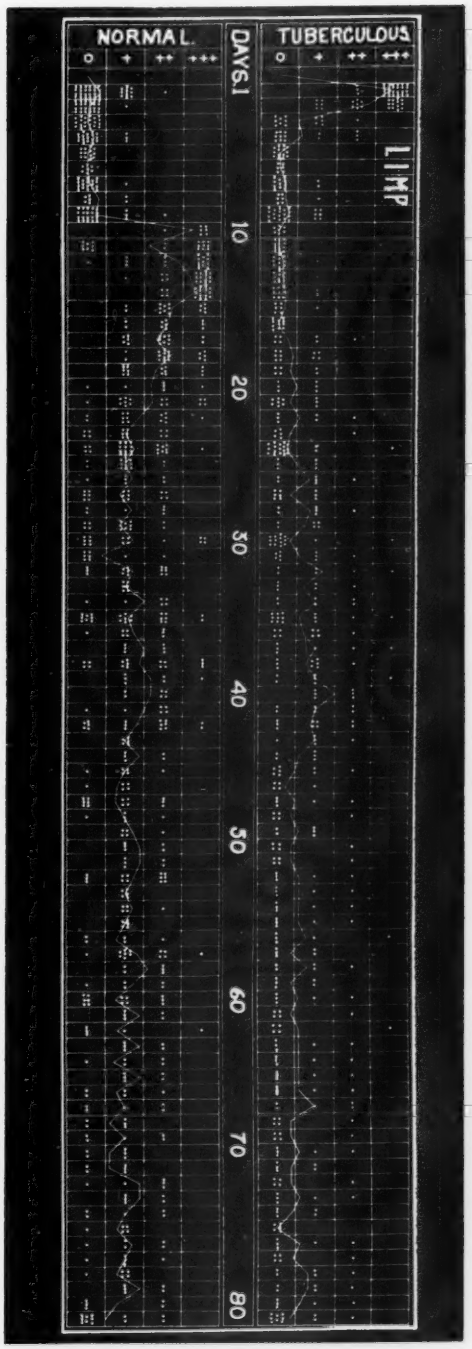

FIG. 3. DEGREE OF LIMP DURING FIRST 81 DAYS RECORDED AS IN FIG. 1

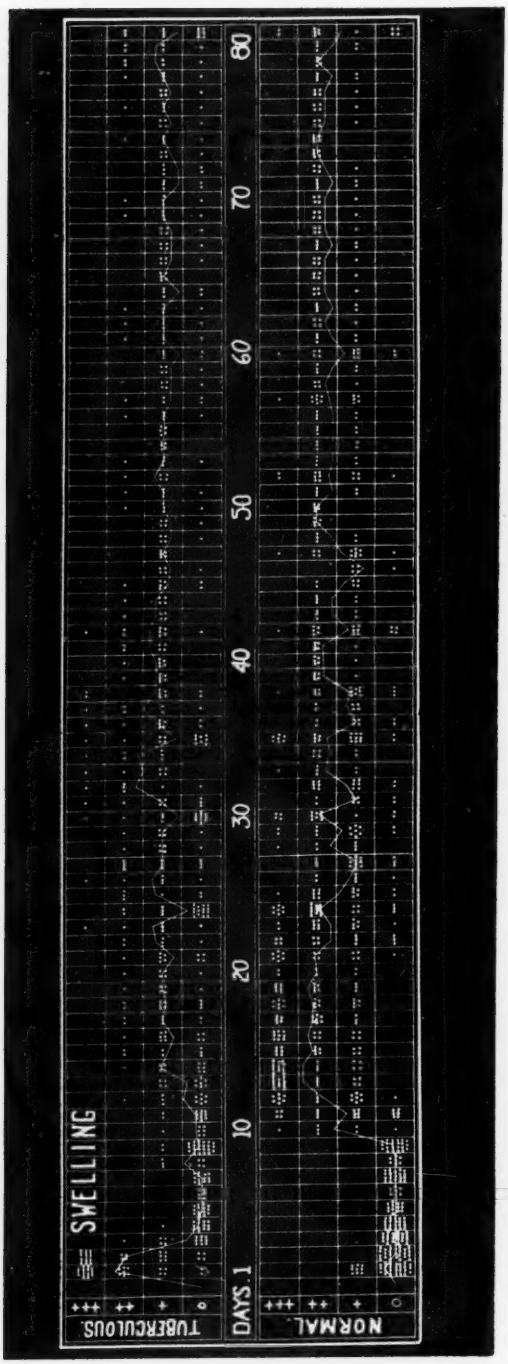

FIG. 4. DEGREE OF SWELLING DURING FIRST 81 DAYS RECORDED AS IN FIG. 1

swelling, were attained the day after the onset of symptoms. In several the maximum limp was reached on the day of onset. This sudden appearance of symptoms can be seen clearly in the individual records, (for instance, figures 5 and 6). In figures 3 and 4 it is obscured because the day of onset of symptoms differed in individual animals.

In this respect there were differences between the groups injected at different times. Unfortunately group NI (see table 1) was not examined clinically between the 9th and the 24th days, so that the onset was missed. The symptoms appeared on the 10th and 11th days in group NIIc, on the 11th and 12th days in group NIII, and on the 8th, 9th and 10th days in group NIV. After the onset of symptoms the groups behaved alike. The notches in the curves in figures 3 and 4 are statistical artefacts.

In an attempt to correlate this recrudescence of symptoms with the appearance of tuberculin sensitiveness, intracutaneous injections of 5 per cent Old Tuberculin were made in the seven surviving members of group NIV, all animals of first infection, on the 8th, 11th and 14th days, a new area being chosen for each injection. On the 8th day all the reactions were negative. On the 11th day mild erythema (3–12 mm.) occurred in all, with slight oedema (3–10 mm.), but without necrosis. On the 14th day all showed erythema (10–20 mm.) and oedema (11–20 mm.). Small central necroses occurred in all but two, and of these one had a small ecchymosis. It would seem that the reappearance of symptoms occurs about at the time of appearance of tuberculin sensitiveness.

After about a week the symptoms in the previously normal group began to diminish gradually, while those in the previously tuberculous animals continued to increase a little. Thus the two groups tended to approach each other and to overlap in increasing degree. However, until the end of the experiment the reinfected animals had symptoms a little less severe, on the average, than the previously normal ones. This difference continued up to the 285th day in those animals of groups TI and NI allowed to survive that long, but with so few animals this is not significant. The fact that the limp appears, from the charts, to improve more than the swelling is meaningless, because the two scales are not comparable.

Figures 5 and 6 show the clinical findings in a pair of animals from groups TIV and NIV respectively. These groups were examined every day for 81 days after the knee injection. The differences pointed out in figures 3 and 4 show even more clearly in these individual records. The

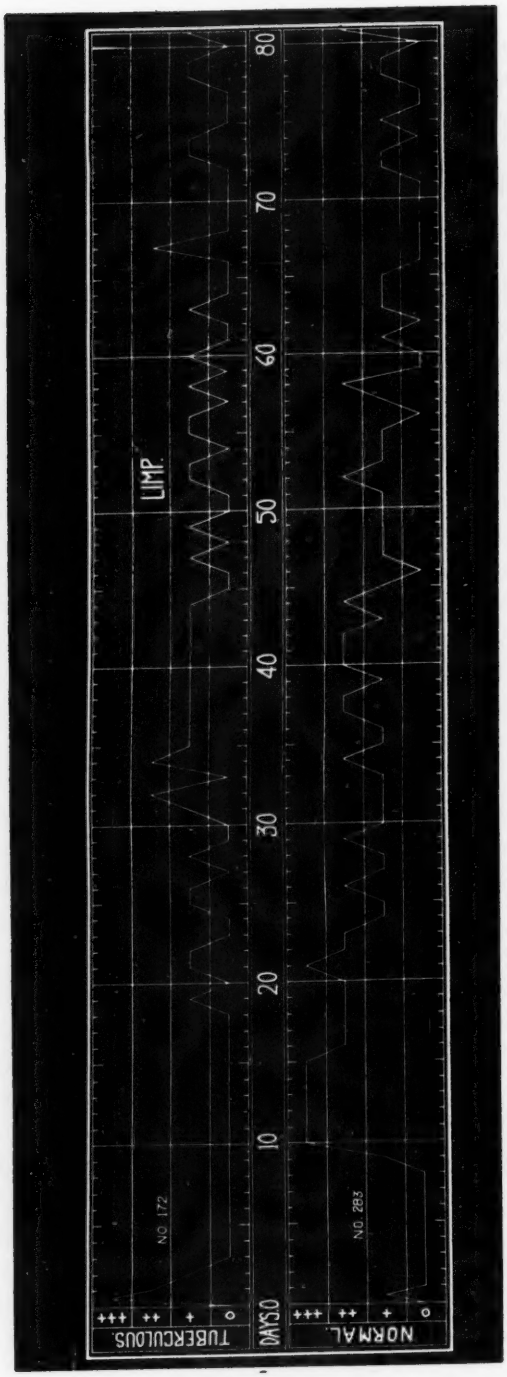

FIG. 5. INDIVIDUAL RECORD OF LIMP SHOWN BY A SINGLE PREVIOUSLY TUBERCULOUS (NO. 172) AND A PREVIOUSLY NORMAL (NO. 283) ANIMAL, EXAMINED DAILY FOR 81 DAYS

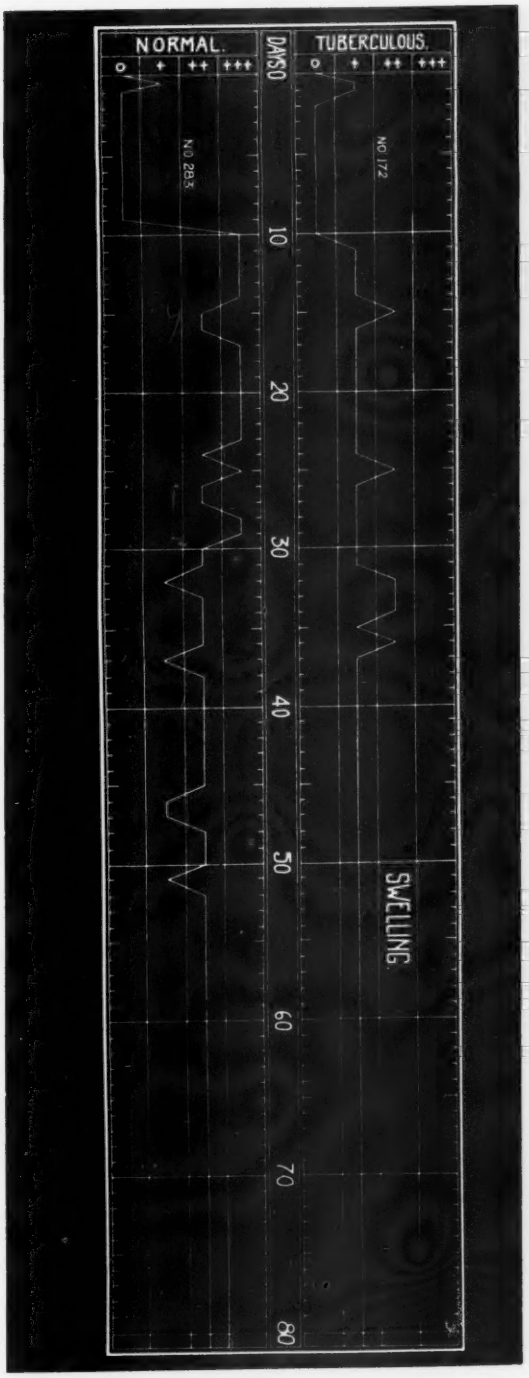

FIG. 6. RECORD OF SWELLING SHOWN BY SAME TWO ANIMALS AS IN FIGURE 5.

degree of fluctuation in severity from day to day is a fair measure of the objectivity of the method of observation. It is highly improbable that the wide daily variations observed correspond to any actual changes in the severity of the lesions. They represent the subjective element which it was impossible to eliminate. As one would expect, this element is greater in the case of limp than in that of swelling.

Anatomical Changes in the Knees

The knees of all the animals were examined grossly. Microscopic sections were made of all except those which survived between 63 and 83 days after the last injection. The findings are recorded in tables 2 and 3. For reasons which will appear the knees in groups TI and NI will be described after the others.

One-half hour after the injections, both the reinfected knees (nos. 125, 129) and those of first injection (nos. 243, 248) appear normal microscopically. Except for a slight dilation of the joint space as if by fluid in nos. 125 and 248 the gross findings correspond.

At 2 hours the previously tuberculous (nos. 126, 130) and the previously normal (nos. 244, 249) animals are again alike, but now all four sections show polymorphonuclear leucocytes infiltrating the subsynovial areolar tissue to a slight degree and in some places forming a layer 3 to 15 cells thick on the surface of the synovia. Occasional groups of them are found lying free in the joint space in a fine meshwork of fibrin (nos. 244, 249).

At 4 hours the cellular infiltration of the subsynovia is a little more dense than before, and the amount of fibrin and the number of leucocytes in the exudate somewhat increased. Aside from congestion of the superficial vessels (nos. 245, 251) or a slight dilation of the joint space (nos. 127, 131) the gross changes are not significant.

At 13 hours the knees of primary (no. 253) and of secondary (no. 134) infection are still alike. In both the fibrinous exudate is sufficiently increased in amount so that fibrin can be seen grossly. Both knees are somewhat swollen and hyperaemic. The exudate contains more leucocytes than before, and among them there are now mononuclears in considerable numbers.

At 24 hours for the first time differences appear between the previously normal (nos. 247, 252) and the reinfected (nos. 128, 133) animals. In the former there has been a distinct subsidence in the severity of the inflammation, and the exudate is greatly reduced in amount, while in the

TABLE 2

*Anatomical changes in the knees of the reinfected animals, recorded on an arbitrary scale**

NUMBER OF ANIMAL	GROUP	INTERVAL BETWEEN INJECTIONS	SURVIVAL AFTER LAST INJECTION	CAUSE OF DEATH	CHANGES IN KNEES							
					Exudate			Synovia				
					Polymorphonuclears	Mononuclears	Fibrin	Polymorphonuclear infiltration†	Mononuclear infiltration†	Granulation tissue	Bone-marrow tubercles	Extension around joint
		days	*hours*									
125	TIIa	36	½	Chloroform	0	0	0	0	0	0	0	0
129	TIIb	70	½	Chloroform	0	0	0	0	0	0	0	0
126	TIIa	36	2	Chloroform	+	0	0	+	0	0	0	0
130	TIIb	70	2	Chloroform	+	0	0	+	0	0	0	0
127	TIIa	36	4	Chloroform	+	0	+	++	0	0	0	0
131	TIIb	70	4	Chloroform	+	0	+	++	0	0	0	0
134	TIIc	77	13	Chloroform	++	+	++	++	+	0	0	0
128	TIIa	36	24	Chloroform	+++	++	+++	+	++	0	0	0
133	TIIb	70	24	Chloroform	+++	++	+++	++	++	+	0	0
			days									
177	TIV	36	5	Chloroform	0	+	+	0	++	+	0	0
135	TIIc	77	10	Chloroform	0	0	+	0	++	++	0	0
138	TIIc	77	11	Chloroform	0	0	+	+	++	++	0	0
102	TI	36	17	Undetermined	0	0	0	0	+	++	0	+
178	TIV	36	17	Chloroform	0	+	+	0	+	++	0	+
139	TIIc	77	21	Chloroform	0	0	0	0	++	++	0	0
110	TI	36	27	Undetermined	0	0	0	0	+	0	0	0
101	TI	36	28	Paratyphoid	0	0	0	0	+	0	0	0
115	TI	36	32	Undetermined	0	0	0	0	+	+	0	0
108	TI	36	41	Paratyphoid	0	0	0	0	++	0	0	++
176	TIV	36	42	Chloroform	0	0	0	0	++	+++	0	++
140	TIIc	77	45	Chloroform	0	+	+	0	++	+++	0	+++
141	TIIc	77	45	Chloroform	0	0	0	0	++	+	0	+
142	TIIc	77	45	Chloroform	0	+	+	0	++	++	+	++
169§	TIV	36	81	Pneumonia			0			++		0
170§	TIV	36	82	Chloroform			0			+++		++
171§	TIV	36	83	Chloroform			0			++		0
172§	TIV	36	83	Chloroform			0			+++		++
175§	TIV	36	83	Chloroform			0			++		++
112	TI	36	92	Undetermined	0	0	0	0	++	++	0	++
111	TI	36	93	Undetermined	0	0	0	0	++	++	0	+
103	TI	36	126	Chloroform	0	0	0	0	++	+++	0	+
107	TI	36	169	Chloroform	0	0	0	0	+	++	0	+
109	TI	36	212	Chloroform	0	0	0	0	++	++	+	++
113	TI	36	284	Chloroform	0	0	0	0	++	+++	+	++
114	TI	36	285	Chloroform	0	0	0	0	++	++	++	++

* The tabular presentation of pathological findings requires an oversimplification which does a certain violence to the facts, which are essentially qualitative and can be clearly understood only from the descriptions.

† The word "infiltration" refers to regions not occupied by granulation tissue. Whenever the latter is present, its cells are predominantly mononuclear.

§ Microscopic section not made.

TABLE 3

*Anatomical changes in the knees of the animals of first infection, recorded on an arbitrary scale**

NUMBER OF ANIMAL	GROUP	SURVIVAL AFTER LAST INJECTION	CAUSE OF DEATH	CHANGES IN KNEES							
				Exudate			Synovia				
				Polymorphonuclears	Mononuclears	Fibrin	Polymorphonuclear infiltration†	Mononuclear infiltration†	Granulation tissue	Bone-marrow tubercles	Extension around joint
		hours									
243	NIIa	½	Chloroform	0	0	0	0	0	0	0	0
248	NIIb	½	Chloroform	0	0	0	0	0	0	0	0
244	NIIa	2	Chloroform	+	0	+	+	0	0	0	0
249	NIIb	2	Chloroform	+	0	+	+	0	0	0	0
245	NIIa	4	Chloroform	+	0	+	++	0	0	0	0
251	NIIb	4	Chloroform	++	0	++	++	+	0	0	0
253	NIIc	13	Chloroform	++	+	++	++	+	0	0	0
247	NIIa	24	Chloroform	+	+	+	0	+	0	0	0
252	NIIb	24	Chloroform	++	++	++	+	+	0	0	0
		days									
273	NIV	5	Chloroform	0	0	+	0	+	0	0	0
255	NIIc	10	Chloroform	+	+	+	+	+	+	0	0
256	NIIc	11	Chloroform	+++	++	+++	+	+	+	0	0
224	NI	17	Undetermined	0	0	0	0	+	0	0	0
274	NIV	17	Chloroform	0	0	++	0	+++	+++	++	++
218	NI	20	Paratyphoid	0	0	+	0	+	0	0	0
257	NIIc	21	Chloroform	+	+	0	+	+++	+++	+	++
221	NI	22	Paratyphoid	0	0	0	0	++	0	0	++
223	NI	37	Paratyphoid	0	+	+	+	+++	+++	+	++
280	NIV	42	Chloroform	0	0	0	0	+++	+++	++	+
259	NIIc	43	Paratyphoid	0	0	0	0	++	+	0	++
258	NIIc	45	Chloroform	0	0	0	0	+++	+++	++	+++
205	NI	48	Undetermined	0	0	0	0	+++	+++	0	+
267§	NIII	63	Chloroform			0			+++		+++
268§	NIII	63	Chloroform			0			+++		0
265§	NIII	64	Chloroform			0**			+++		+++
266§	NIII	64	Chloroform			0			+++		++
261§	NIII	66	Chloroform			0			+++		+++
262§	NIII	66	Chloroform			0			+++		++
263§	NIII	66	Chloroform			0			+++		++
264§	NIII	66	Chloroform			0			+++		++
279§	NIV	81	Chloroform			0			+++		+++
281§	NIV	82	Chloroform			0			+++		+++
282§	NIV	83	Chloroform			0			+++		+++
283§	NIV	83	Chloroform			0**			+++		++
284§	NIV	83	Chloroform			0			+++		++
222	NI	126	Chloroform	0	0	0	0	++	++	+	++
206	NI	169	Chloroform	0	0	0	0	++	+++	+	+

TABLE 3—*Concluded*

NUMBER OF ANIMAL	GROUP	SURVIVAL AFTER LAST INJECTION	CAUSE OF DEATH	CHANGES IN KNEES							
				Exudate			Synovia			Bone-marrow tubercles	Extension around joint
				Polymorphonuclears	Mononuclears	Fibrin	Polymorphonuclear infiltration†	Mononuclear infiltration†	Granulation tissue		
		days									
204	NI	212	Chloroform	0	0	0	0	++	+++	+	+
216	NI	284	Chloroform	0	0	0	0	++	+	+	0
217	NI	285	Chloroform	0	+	+	0	+	+++	+	++
219	NI	285	Chloroform	0	0	0	0	+++	+++	++	+
220	NI	285	Chloroform	0	0	0	0	+++	+++	++	+++

* The tabular presentation of pathological data requires an oversimplification which does a certain violence to the facts, which are essentially qualitative and can be clearly understood only from the descriptions.

† The word "infiltration" refers to regions not occupied by granulation tissue. Whenever the latter is present, its cells are predominantly mononuclear.

§ Microscopic section not made.

** The joint cavity contains caseous débris.

previously tuberculous animals the amount of fibrin and the number of cells are markedly increased. In both cases the polymorphonuclears still predominate, but there are many mononuclears, particularly attached to the synovial lining. The microscopic differences are quantitative rather than qualitative. The gross findings correspond roughly. Both of the reinfected animals show swelling, one (no. 133) to a marked degree, while only one of the others (no. 247) shows any. There was somewhat more fibrin in the reinfected animals than in the others. Dilation of the joint cavity was found only in one of the animals of first infection (no. 247).

At 5 days the polymorphonuclear infiltration has completely subsided in both sections. In the reinfected animal (no. 177) the serosa has been entirely replaced by a layer of tissue containing fibrin and many mononuclear cells. In some places the latter have small rather dark nuclei, but in others, particularly where there is much unorganized fibrin adherent, they have large pale oval nuclei and a rather irregular acidophilic cytoplasm. In such places there is a characteristic tuberculous granulation tissue. In the animal of first infection (no. 273) there is hardly any fibrin, and the abnormal findings are confined to a slightly excessive number of mononuclears in and immediately beneath the synovial lining.

In many places the synovia is normal. Grossly no. 177 shows swelling, free fibrin and definite but slight thickening of the synovia. Of these only the last finding is present also in no. 273, which is otherwise normal in the gross.

At 10 days the secondarily infected knee (no. 135) is very similar to that at 5 days, except that there is less free fibrin. The primarily infected animal (no. 255) was killed one day after its last clinical examination. At that time clinical symptoms had not yet reappeared. The section shows here and there a layer of granulation tissue similar to but thinner than that of no. 135. Occasionally a few polymorphonuclears are found in the synovia. There are also a few shreds of free fibrin. Grossly both animals show dilation of the joint space and fibrin, but only no. 135 is swollen and hyperaemic.

The pair of animals autopsied on the 11th day was killed after the reappearance of symptoms (limp $+++$, swelling $+$) in the previously normal animal no. 256). With the skin removed the injected knees of both guinea pigs are seen to be swollen, but that of no. 256 more severely. This knee is somewhat hyperaemic. Both joint cavities are dilated, but this is more marked in the reinfected animal (no. 138). Fibrin is visible grossly in both joints, but that of no. 256 contains far more. Microscopically the reinfected knee is very much like that at 10 days. There are occasional Langhans giant cells and small areas of incipient necrosis. Polymorphonuclears are exceedingly rare, and there is no free fibrin visible in the section. The knee of no. 256 shows the same changes as that of no. 255 (at 10 days), but in addition there is a great deal of fibrinous exudate densely packed with polymorphonuclear cells, with a good many mononuclears as well.

At 17 days (neglecting for the present the members of groups TI and NI) the sensitized animal (no. 178) showed a rather extensive synovial granulation tissue with epithelioid cells, involving the areolar tissue to some extent. There is no necrosis. Grossly there is only a slight swelling and a slight thickening of the synovia. The previously normal animal (no. 274) shows by far the severest changes so far described. There is slight hyperaemia, marked swelling, dilation of the joint space, free fibrin and thick synovial granulation tissue. Microscopically the latter is found to involve the synovial lining and all the subsynovial areolar tissue, and to extend far up among the fibres of the quadriceps muscles. Both the tibia and the femur contain small epiphyseal tubercles, that in the femur being continuous with the synovial changes

through one of the small openings, which in guinea pigs occur normally at the attachments of the cruciate ligaments. For the first time tuberculous changes can be seen grossly in the adjacent tissues outside the joint.

At 21 days the gross differences between the reinfected (no. 139) and the primarily infected (no. 257) animals are similar to those at 17 days. Microscopically no. 139 shows a granulation tissue similar to that of no. 178 (at 17 days), but a little more extensive. There is no necrosis and only slight involvement of the subsynovial areolar tissue. In no. 257 the synovia is entirely replaced by a thick tuberculous granulation tissue, which involves the subsynovia and extends far into the quadriceps and the posterior tibial muscles. Necrotic foci are found in all three places. The marrow of the tibial epiphysis contains a single tubercle, which is continuous with the synovial granulation tissue at the insertion of one of the cruciate ligaments.

Between the 42nd day and the 45th there are no significant differences, either grossly or microscopically, in the degree or kind of synovial disease shown by the reinfected (nos. 176, 140, 141, 142) and the previously normal (nos. 280, 259, 258) animals. In all a granulation tissue involves the synovia, the underlying areolar tissue and the quadriceps muscles to some extent. This tissue contains more collagen than that found in the previous sections, and also more lymphocytes and mature connective-tissue cells. The only significant difference between the two groups is in the degree of bone-marrow involvement. Two (nos. 280, 258) out of three of the previously normal guinea pigs show tubercles in the epiphyseal marrow of both tibia and femur, while of the four reinfected animals only one (no. 142) shows any marrow involvement, and this consists of a single small tubercle in the tibial epiphysis. Number 280 also shows a small tubercle lying in a subperiosteal opening in the cortex of the femoral shaft. With two exceptions (nos. 141, 280), granulation tissue is visible grossly outside the joint in every case in both groups.

All the animals autopsied between the 63rd day and the 66th belong to the previously normal group (NIII). Microscopic sections were not made of these knees. Grossly all are swollen and all but one (no. 263) hyperaemic. The synovia shows granulations in every case. In one animal (no. 265) the joint cavity is filled with caseous debris. Definite erosion of the cartilage occurs in only two (nos. 265, 268). Extension of the process to the tissues around the joint is seen in all but one (no. 268), and is sufficient in one animal (no. 265) to cause several collections of pus, of which the largest is 1.5 cm. in diameter.

Of the animals killed between the 81st day and the 83rd no microscopic sections were made. The gross changes are qualitatively alike in the two groups, with fairly wide variations among the individual animals. The average severity is definitely greater in the previously normal than in the reinfected group. The extent of the lesions corresponds roughly to the severity of the symptoms at the last clinical examination before death. All show swelling of some degree, and most are hyperaemic. Synovial granulations are present in all cases, with a slight excess of fluid in half (nos. 171, 172, 175, 282, 283). The cartilage is slightly eroded in three (nos. 279, 281, 282), all animals of first infection. All of the primarily infected guinea pigs and three of the reinfected ones (nos. 170, 172, 175) have gross lesions outside the joint. In one (no. 279) acid-fast bacilli were demonstrated here by a smear.

The members of groups TI and NI will now be given separate consideration, since the findings differed in some respects from those in the other groups.

At 17 days the previously tuberculous animal (no. 102) is very much like the corresponding animal in group TIV (no. 178), both in the gross and in the microscopic picture, except that the granulation tissue in no. 102 contains fewer epithelioid cells and a far greater number of round cells. The previously normal guinea pig (no. 224), however, in contrast to the severe changes in no. 274, shows nothing but a slight hyperplasia of the serosal cells with a small mass of fibrin adherent to the serosa in one place. The gross findings are normal. The difference between this knee and that of the other previously normal animal autopsied after the same time-interval is therefore extreme. The same paucity of abnormal findings in the knees of the guinea pigs of first infection occurs at 20 (no. 218) and at 22 (no. 221) days, a marked difference from the findings at the corresponding interval of 21 days (no. 257) in group NIIc.

At 27 (no. 110), 28 (no. 101), 32 (no. 115) and 41 (no. 108) days the reinfected knees of group TI show great evidence of improvement. The abnormal findings are practically limited to nodular collections of lymphocytes and mononuclears in the synovia, far less extensive than the changes at 17 days (no. 102). There are occasional shreds of fibrin, visible microscopically on the serosal surface in no. 115. The gross appearance is normal. In the animals of first infection the changes at 37 (no. 223) and at 48 (no. 205) days are in marked contrast to those up to 22 days. There is extensive tuberculous granulation tissue with necrosis, involving all synovial layers and extending outside the joint.

Number 223 presents a microscopic tubercle in the marrow of the tibial epiphysis. These sections are in every respect similar to those in the other primarily infected groups at the corresponding time-interval.

It is unfortunate that groups TI and NI were not examined clinically between the 9th and the 24th days. At the latter time the symptoms in group NI were well developed. The microscopic sections indicate that in the members of this group autopsied up to the 22nd day severe lesions had not yet developed. This suggests that the interval before the reappearance of symptoms was at least twice as long as that in any other group. A fact of interest in this connection is that at 24, 30 and 35 days (see figures 3 and 4) the symptoms in group TI, which received the same suspension, were on the average definitely less severe than those in the other reinfected groups. Perhaps the number of living bacilli in the suspension given groups TI and NI was less than in the others. The total number of bacilli injected was not significantly different.

All the animals autopsied from the 92nd day on belonged to groups TI or NI. On the 92nd (no. 112) and the 93rd (no. 111) days both guinea pigs were reinfected ones. Both show a fairly well-organized granulation tissue with many lymphocytes and mature connective-tissue cells. This tissue extends well outside the joint into the region above the patella. The bone-marrow is not involved.

From the 126th to the 285th day the synovial lesions do not change significantly in character or extent, though there are individual variations. There is an extensive granulation tissue replacing the whole synovial lining, extending into the subsynovial areolar tissue and outside the joint. In many places there are epithelioid cells, round cells and occasional giant cells. Necrosis is rare, but small areas are seen occasionally. In some places there are no characteristic epithelioid cells, but many fibroblasts. In all the sections there are more collagen fibres than in earlier ones. In some places these have been laid down in sufficient numbers to form a rather dense fibrous tissue with many mature connective-tissue cells. In such places the tissue loses its distinctively tuberculous appearance. In tables 2 and 3 this tissue is still called "granulation tissue." The reinfected group cannot be distinguished from the previously normal, either grossly or microscopically, except for the marrow lesions. These are absent in the reinfected animals at 126 (no. 103) and at 169 (no. 107) days, but are present in the epiphyses of the long bones in all the remaining members of the group. In the primarily infected animals such lesions are found in all the sections from the 126th

TABLE 4

Autopsy findings. Degree of enlargement of lymph nodes and extent of visceral tuberculosis recorded on an arbitrary scale

ANIMAL NO.	GROUP	INTERVAL	SURVIVAL	CAUSE OF DEATH	MACROSCOPIC TUBERCULOSIS						
					Left inguinal lymph nodes	Right inguinal lymph nodes	Retroperitoneal lymph nodes	Bronchial lymph nodes	Spleen	Liver	Lungs
		days	*days*								
102	TI	36	17	Undetermined	+	+++	+		0	0	0
110	TI	36	27	Undetermined	+	+++	+	0	0*	0	0
101	TI	36	28	Paratyphoid	+	+	+	0	++*	+	0
115	TI	36	32	Undetermined	++	++	0	++	0	0	++*
108	TI	36	41	Paratyphoid	+++	++	0	++	0*	0	0
176	TIV	36	42	Chloroform	+	+	++	++	0	0*	0*
140	TII	77	45	Chloroform	+	+	++	+	0*	0*	0
141	TII	77	45	Chloroform	+	+	+	+	0	0	0
142	TII	77	45	Chloroform	++	+	++	+	0	0*	0
169	TIV	36	81	Pneumonia	0	+++	+	+	0	0	0*
170	TIV	36	82	Chloroform	++	+++	++	+	+++*	0*	+++
171	TIV	36	83	Chloroform	+	+++	0	+	0*	0*	+
172	TIV	36	83	Chloroform	++	++	++	++	0*	0*	++
175	TIV	36	83	Chloroform	++	++	++	+	++*	+*	++
112	TI	36	92	Undetermined	++	++	++	0	0	0	0
111	TI	36	93	Undetermined	++	+	+	+	0	0*	+
103	TI	36	126	Chloroform	++	++	++	++	++*	0*	0
107	TI	36	169	Chloroform	++	+++	++	++	0*	+*	0*
109	TI	36	212	Chloroform	++	+++	++	+	++*	+*	++*
113	TI	36	284	Chloroform	++	0	++	++	0*	0*	++
114	TI	36	285	Chloroform	++	++	++	+	0*	0*	++
224	NI	—	17	Undetermined	0	0	0	0	++*	0	0
218	NI	—	20	Paratyphoid	+	+	0	0	0	0*	0
221	NI	—	22	Paratyphoid	+	+	+	+	++*	++*	0
223	NI	—	37	Paratyphoid	++	++	++	0	+*	0*	0
280	NIV	—	42	Chloroform	+	+	++	+	+++*	+*	++
259	NII	—	43	Paratyphoid	+	+	++	+	0*	++	+++
258	NII	—	45	Chloroform	+	++	++	+	0	0	0
205	NI	—	48	Undetermined	++	+	++	0	0	+*	0
279	NIV	—	81	Chloroform	+++	0	++	+	++	++*	++
281	NIV	—	82	Chloroform	++	0	++	++	++*	0*	+
282	NIV	—	83	Chloroform	++	+++	+++	++	+++	0*	++
283	NIV	—	83	Chloroform	++	+	+++	++	0*	0	+++
284	NIV	—	83	Chloroform	++	+	++	++	++*	0*	+++
222	NI	—	126	Chloroform	++	+	++	++	0	++	0
206	NI	—	169	Chloroform	++	++	++	++	0*	0*	0*
204	NI	—	212	Chloroform	++	++	+	+	+*	0*	+
216	NI	—	284	Chloroform	++	++	++	++	++*	+*	++
217	NI	—	285	Chloroform	++	++	++	++	++*	0	++
219	NI	—	285	Chloroform	+	++	++	+	++*	0	++*
220	NI	—	285	Chloroform	++	++	++	+	0	0	++

* Microscopic section made to verify diagnosis.

to the 285th days. At 285 days tubercles are found in the patella in the one reinfected (no. 114) and in two (nos. 219, 220) out of three previously normal guinea pigs. Number 220 shows a tubercle at the femoral metaphysis. With one exception (no. 280, at 42 days), already mentioned, the bone lesions in all earlier sections are limited to the epiphyses.

Summary of Changes in the Knees

To summarize, both groups began with an exudation of fibrin and polymorphonuclear leucocytes, which in the reinfected group reached its maximum at 24 hours, at which time it showed definite signs of subsidence in the previously normal animals. Mononuclears were found in both groups from 13 hours onward, increasing in relative numbers so as almost to exclude the polymorphonuclears at 5 days.

The severity of involvement remained greater in the reinfected animals than in the others until the time of reappearance of clinical symptoms in the previously normal ones (about 10 days in groups NIIc and NIV, and probably twice as late in group NI). At this time polymorphonuclears reappeared in the previously normal animals with a new exudation of fibrin. Thereafter the lesions remained on the average more severe in the animals of first infection than in the others, though the difference became decreasingly sharp, disappearing completely on the 285th day.

Degree of General Tuberculosis

In table 4 are recorded the degree of lymph-node enlargement and of macroscopic visceral tuberculosis found in those animals in which complete autopsies were performed. It can be seen that until the 83rd day the extent of visceral tuberculosis appears to have been slightly greater in the previously normal than in the previously tuberculous animals, whereas after this time there was no significant difference. With the exception of the right inguinal lymph nodes, where the previously tuberculous animals showed the greater involvement, there were no differences in the degree of lymph-node enlargement. These findings are consistent with the belief that the sensitized animals were slightly more resistant to a subsequent tuberculous infection than were the previously normal ones.

SUMMARY

Following a single measured dose of tubercle bacilli, injected into the knee joint, tuberculous guinea pigs showed clinically an immediate in-

flammatory reaction more severe and of longer duration than that shown by normal animals.

Between the eighth and the twelfth days in most animals, but considerably later in one group, the previously normal guinea pigs developed a second joint inflammation, severe and of sudden onset.

This was simultaneous with the appearance of tuberculin sensitiveness in the one group tested.

The symptoms of inflammation recurred also in the previously sensitized animals, but much more gradually and on the average later.

The accompanying pathological changes corresponded to the clinical findings.

Almost to the end of the experiment the average severity of joint involvement remained somewhat greater in the previously normal animals, though the two groups overlapped widely.

Until the 83rd day the extent of visceral tuberculosis was slightly greater in the previously normal group.

CONCLUSION

The response of the guinea pig's knee joint to tuberculous infection, primary or secondary, is essentially similar to that reported in other tissues.

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THE LEUCOCYTIC REACTION IN TUBERCULOSIS PATIENTS RECEIVING ARTIFICIAL PNEUMOTHORAX

E. M. MEDLAR AND G. S. PESQUERA[1]

The use of artificial pneumothorax in suitable cases of pulmonary tuberculosis is now recognized as a very valuable therapeutic procedure to the physician who has tuberculous cases under his care. There is at present no unanimity of opinion as to when such treatment should be instituted. The efficiency of compression therapy is judged entirely by the X-ray and the clinical results obtained. The use of other means of pulmonary collapse, such as phrenicectomy, pneumolysis or thoracoplasty, is considered only after failure to obtain collapse by artificial pneumothorax, or after the collapse obtained has failed clinically to arrest the disease. This report will give the results of a study of the leucocytic reactions in cases given artificial pneumothorax. The study has suggested to us the use of the leucocytic picture in tuberculous cases as a valuable clinical aid in reaching a decision as to when to institute such treatment and when to use additional methods of collapse therapy.

Our study was begun in 1927. At this time weekly total and differential leucocyte counts were made on cases already under collapse therapy. More recently weekly counts have been done for at least a month before the collapse therapy was begun. In the cases included in this report information concerning the leucocytic reaction was withheld from the one in charge of the pneumothorax cases so that the type of leucocytic response has had no influence upon either the use or the continuance of the collapse therapy. To date 20 cases have been followed for over a year, some of which have been carefully studied for three years. All of the cases have been given pneumothorax because of an exacerbation of the clinical symptoms, of the occurrence of a severe haemorrhage, or of a spread of the tuberculous process within the pulmonary tissues, as shown by physical findings and roentgenographs. In the group four patients have had phrenicectomy in addition to pneumothorax, two have had

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pneumolysis, and one is now being considered for thoracoplasty. Two cases have died.

To illustrate the different types of the leucocytic reaction as found in the group, 6 cases have been selected. Two of these cases show an ineffective pneumothorax, two cases have had a long period of distinct clinical improvement with a subsequent relapse, and two cases have shown and have maintained marked clinical improvement. Below are given brief clinical abstracts, roentgenograph records, and leucocyte charts of these cases.

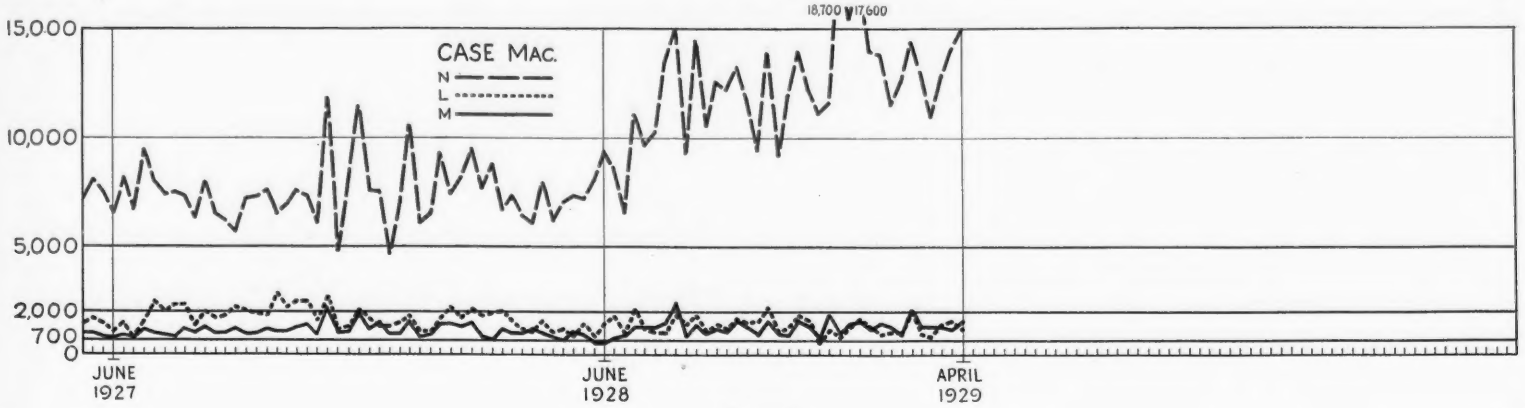
Case Mac.: Female, aged 24. *Past History:* Usual childhood diseases; enlarged thyroid since childhood; attack of "grippe" three years previous to present illness. *Present Illness:* During summer of 1926 patient was easily fatigued; in October cough with expectoration developed; in November had an attack of dry pleurisy; physical examination at this time revealed an involvement of the left apex; roentgenographs showed a dense infiltration of the left upper lobe. Patient was admitted to the Sanatorium December 6, 1926; at this time physical signs were present at the left apex, posteriorly, and over the lower two-thirds of the chest anteriorly; roentgenographs revealed a dense infiltration of the upper two-thirds of the left lung; weight was 3 per cent above normal; sputum positive for tubercle bacilli (Gaffky II); the temperature ranged between 99° and 101°; the pulse varied between 80 and 108.

March, 1927: General dietetic and hygienic treatment with absolute bed-rest has been given; symptoms have persisted and patient has been very toxic; temperature has ranged from 99° to 104°; pulse has varied from 90 to 120; weight has rapidly decreased; sputum has remained positive; artificial pneumothorax was begun.

June, 1927: After the first few injections of gas a spontaneous pneumothorax developed with increased intrathoracic pressure and a displacement of the mediastinum to the right; pneumothorax was discontinued because of this complication; roentgenographs showed the presence of fluid; patient had become critically ill; loss of 20 kg. in weight had occurred.

June, 1928: Steady clinical improvement has occurred; there has been a gain of 22 kg. in weight; symptoms have diminished, although cough and expectoration are present; sputum negative for tubercle bacilli for past eight months; temperature has returned to normal; pulse-rate decreased but is still above normal; there are physical signs over the upper third of the right lung.

April, 1929: A tuberculous empyema and a bronchial fistula have developed on the left side. A study of the fluid from the left pleural cavity showed a large number of tubercle bacilli and no other organisms. Rapidly spreading tuberculosis with cavitation has developed in the right lung. Clinical symptoms have become marked and the patient has steadily lost ground; death occurred in April, 1929.


15,000
10,000
5,000
2,000
700
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CASE MAC.
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17,600
JUNE
1927
JUNE
1928
APRIL
1929

CHART 1

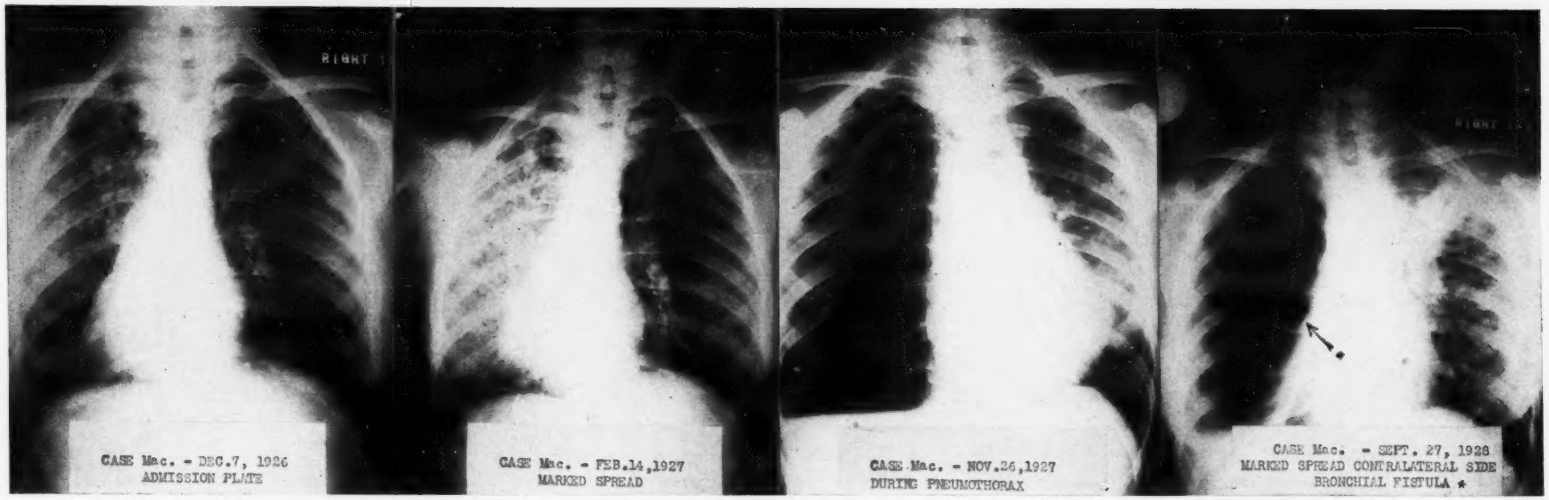

RIGHT
CASE Mac. - DEC.7, 1926
ADMISSION PLATE
CASE Mac. - FEB.14,1927
MARKED SPREAD
CASE Mac. - NOV.26,1927
DURING PNEUMOTHORAX
CASE Mac. - SEPT. 27, 1928
MARKED SPREAD CONTRALATERAL SIDE
BRONCHIAL FISTULA *

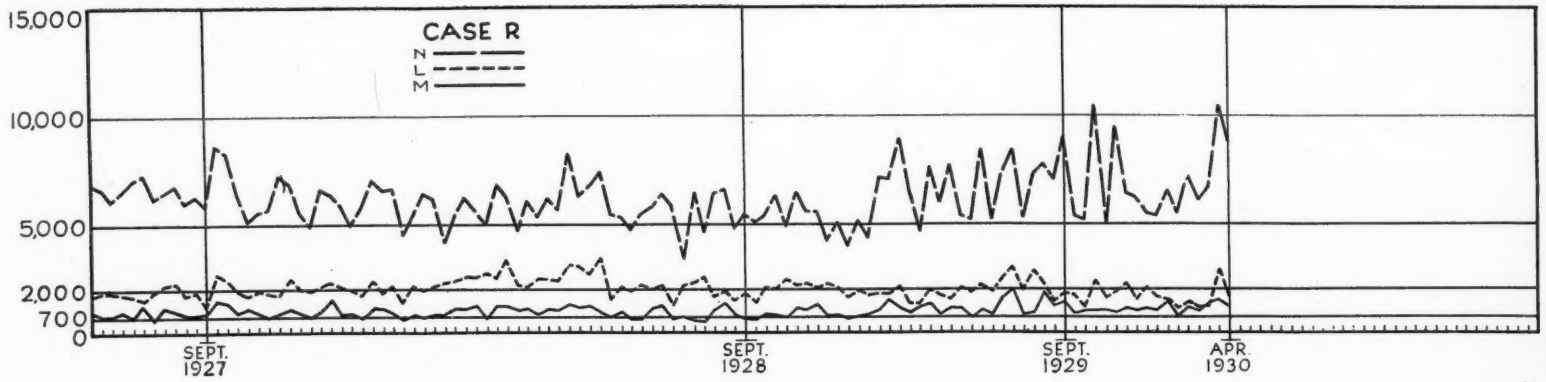
FIG. 1

The leucocytic graph of this case is instructive. At no time was there any evidence of an actual improvement in the tuberculous process, although there had occurred a considerable period of decided clinical improvement. During the entire period of study the neutrophiles dropped to the upper limit of normal on but two occasions; the lymphocytes rose above the lower limit of normal on but nine occasions; and the mononuclear leucocytes were above the upper limit of normal in all but four counts. There was evidence of a spread of the tuberculous process with greater involvement of tissue. The leucocytic reaction demonstrated this for a considerable length of time before a marked exacerbation of clinical symptoms occurred. Note the numerous times in which the lymphocytes and the mononuclear leucocytes have crossed. This case had a high monocyte-lymphocyte ratio, which is in accord with the observations of Cunningham, *et al.* (1), of Blackfan (2), and of others. Note, also, that the neutrophiles were always increased, and that as the disease progressed they became more and more the dominant cell in the leucocytic picture. The neutrophile must not be ignored in the leucocytic reaction as found in the tuberculous. It is the essential cell in the formation of the uncontaminated tuberculous abscess. It is when such abscesses rupture that "spreads," haemorrhages, etc., occur. This graph represents the leucocytic response in a case of a tuberculous infection with a progressive course and a fatal outcome. Taking the case as a whole, the leucocytic reaction proved to be a better indicator of the actual status of the pathological process than were the other clinical data.

Case R.: Female, aged 20. *Past History:* Measles and diphtheria in childhood; "grippe" in 1924. *Present Illness:* Symptoms, characterized by coryza, cough and lack of endurance, appeared in January, 1926. The symptoms became progressively worse and expectoration, purulent in type, developed. Early in June patient had an attack of "grippe" with a temperature of 101°; symptoms persisted for a month; physical examination at this time gave signs over the upper lobes of both lungs; roentgenographs showed an involvement of the upper right lung with cavitation.

Patient admitted to Sanatorium June 30, 1926. Sputum positive for tubercle bacilli; pulse varied from 60 to 90; temperature ranged from 98° to 99.4°; weight was 6 per cent below normal.

January, 1927: Under general hygienic and dietetic treatment, with absolute bed-rest, the symptoms have improved; pulse and temperature have returned to normal. From physical findings and roentgenographs the case was regarded as definitely improved. Weight has increased to 5 kg. above normal; sputum negative on most of the examinations. Because of a death in


CASE R
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10,000
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SEPT. 1927
SEPT. 1928
SEPT. 1929
APR. 1930

CHART 2

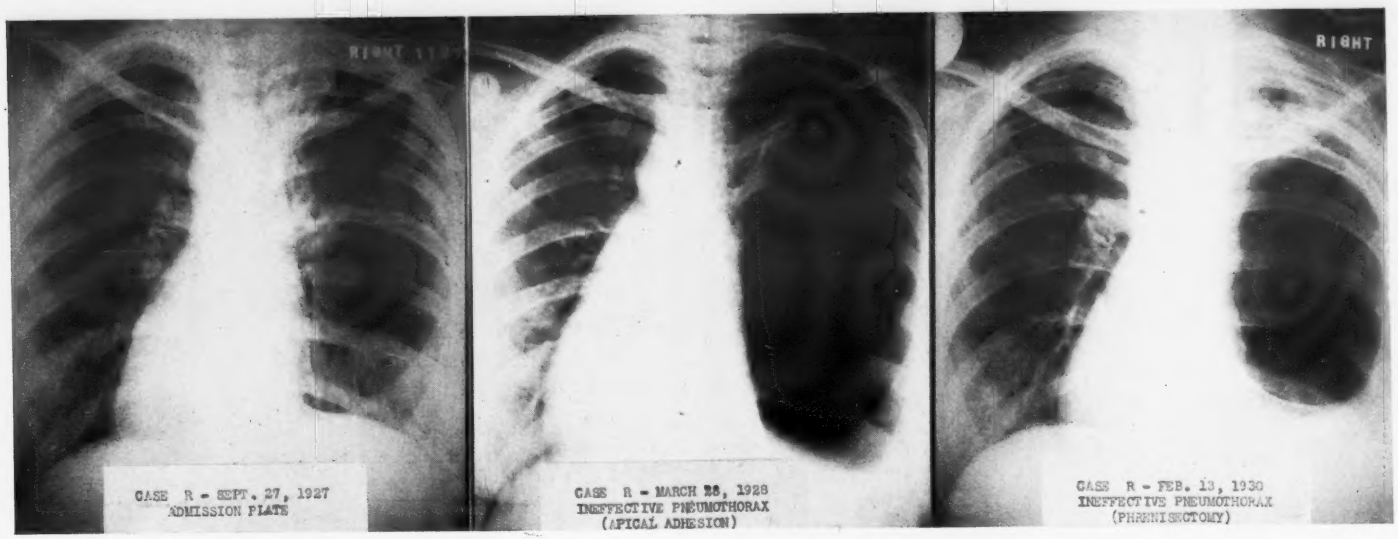

CASE R - SEPT. 27, 1927
ADMISSION PLATE
CASE R - MARCH 28, 1928
INEFFECTIVE PNEUMOTHORAX
(APICAL ADHESION)
RIGHT
CASE R - FEB. 13, 1930
INEFFECTIVE PNEUMOTHORAX
(PHRENICECTOMY)

FIG. 2

the family patient was allowed a two weeks' leave of absence, during which time a haemorrhage occurred and the sputum was blood-streaked for three days.

April, 1927: Symptoms have reappeared; temperature and pulse have remained normal; physical signs have increased.

September, 1927: Symptoms have again improved; physical findings are less; sputum has become negative for tubercle bacilli; weight remains above normal; pulse and temperature normal. Exercise was begun; sputum became blood-streaked; pulse-rate increased; roentgenograph showed a distinct increase and collapse therapy was begun.

September, 1928: Complete collapse has not been obtained because of extensive adhesions at the apex; definite clinical improvement has occurred; weight remains above normal; there is no expectoration; pulse and temperature remain normal. Exercise was begun again, with the result that the lung reëxpanded and cough and expectoration again appeared. The sputum has become positive for tubercle bacilli; pulse-rate has increased to 100; temperature has remained normal. Patient was again confined to bed and treatments were given at shorter intervals; this caused a disappearance of symptoms; physical signs reappeared at the apex; roentgenographs showed a gradual reëxpansion of the lung and enlargement of the cavity in spite of the collapse therapy.

September, 1929: Patient has been confined to bed, with bathroom privileges. There has been no clinical improvement; sputum is present and positive for tubercle bacilli; blood-streaks are present in the sputum during the menstrual period; pulse ranges between 80 and 100; temperature remains normal.

April, 1930: There has been no clinical improvement; physical findings are more marked; roentgenographs show a collapse of the middle third of the lung. A phrenicectomy has been done preparatory to a thoracoplasty, which the patient refuses to have done at the present time.

This is a case in which pneumothorax appeared to be effective while the patient was confined strictly to bed. On attempted exercise the beneficial effect of the pneumothorax was found to be more apparent than real. Because of the extensive apical adhesions a satisfactory collapse could not be obtained and the extent of the adhesions rendered pneumolysis impossible.

The leucocytic graph of this case again shows the septic type of leucocytic reaction. At times there has been a tendency for the neutrophiles to come within normal range. This has always been temporary in nature, and for the past several months the neutrophiles have remained constantly above normal. For a time the lymphocytes stayed well above the lower limit of normal, but of late there has occurred a marked drop. The mononuclears have tended, on the whole, to remain above

normal. This case has shown no consistent tendency to heal the tuberculous process. From the leucocytic picture one may judge that the condition is worse now than it has ever been. Pneumothorax and bed-rest undoubtedly account for the changing of the leucocytic reaction slightly toward a healing phase, but on the whole the leucocytes reveal, as do the other clinical findings in the case, that to date all efforts to check the progress of the disease have been futile. In brief, one may judge from the leucocytic graph that this is a case of ulcerating, progressive tuberculosis.

Case B.: Female, aged 19. *Past History:* Measles, pertussis and chicken-pox in infancy; "grippe" in 1918. *Present Illness:* Onset was insidious with loss of strength and of weight; on January 6, 1926, a small haemorrhage occurred, followed by blood-streaked sputum and fever; physical signs were indefinite; roentgenograph showed an infiltration of the right upper lobe and a small area of increased density at the apex of the left lower lobe.

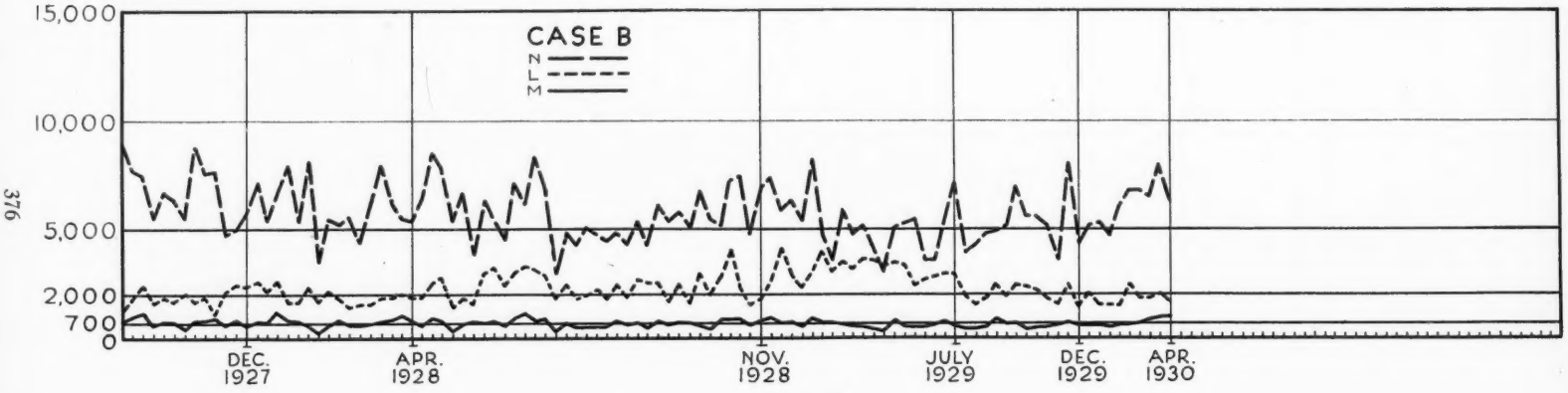
Patient admitted to Sanatorium in March, 1926. Slight cough and expectoration were present; weight 20 per cent below normal; temperature normal; pulse ranged between 70 and 90; sputum negative for tubercle bacilli; physical signs were present over the right upper lobe and at the left apex; roentgenographs showed parenchymatous infiltration throughout the right side, with the greatest involvement in the middle third; a small area of infiltration at the left apex and one at the left base were also noted.

January, 1927: Patient has remained free from symptoms; physical signs have diminished; roentgenographs show some clearing; gain of 7.4 kg. in weight; sputum positive for tubercle bacilli in June; no expectoration at present time; exercise has been taken without untoward effect.

December, 1927: Patient has remained free from symptoms. There has been a gradual increase in physical signs; weight has remained stationary; pulse and temperature have remained normal; roentgenographs, on the whole, have been regarded as favorable.

April, 1928: Physical findings have persisted; expectoration has reappeared and sputum is positive for tubercle bacilli; a steady decline in weight has been recorded; pulse and temperature have remained normal; collapse therapy was begun April 23.

November, 1928: No definite improvement has occurred as a result of the pneumothorax; patient has remained in bed; with each injection of gas there has been a rise in pulse-rate and temperature; sputum has remained positive for tubercle bacilli; there has been a further loss in weight; roentgenograph shows a large adhesion which prevents closure of the cavity; pneumolysis was done which allowed complete collapse of the cavity. Following the pneumoly-


CASE B
N
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15,000
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DEC. 1927
APR. 1928
NOV. 1928
JULY 1929
DEC. 1929
APR. 1930

CHART 3

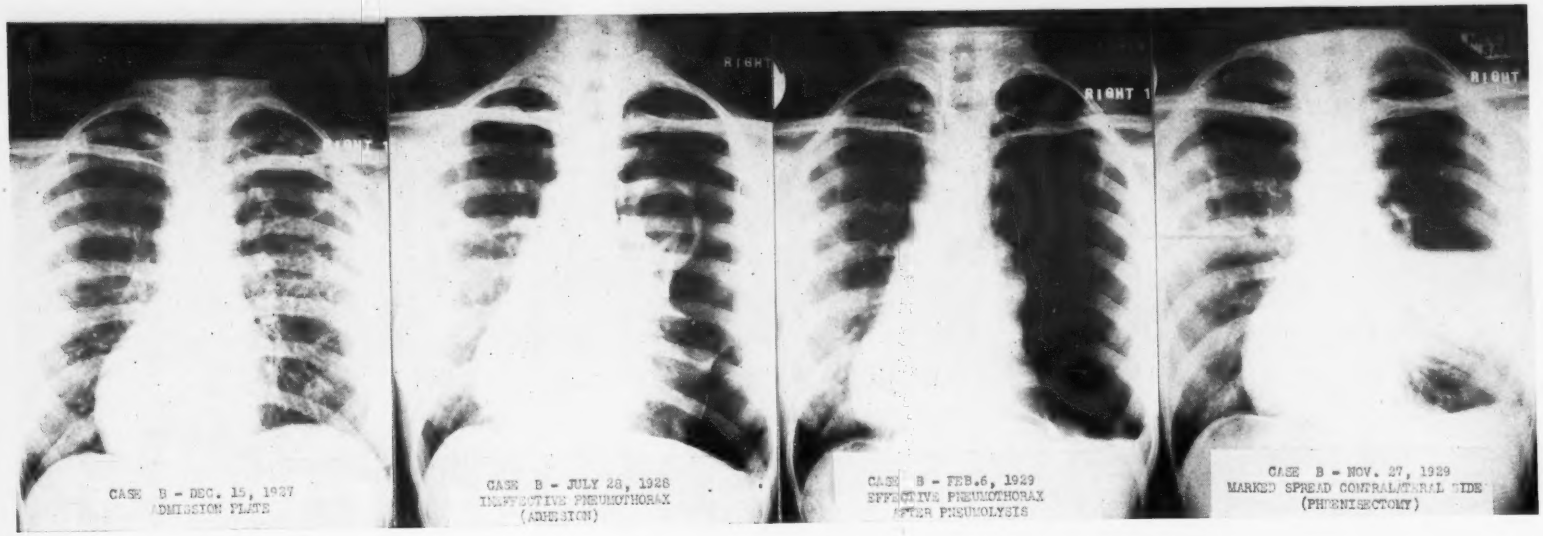

CASE B - DEC. 15, 1927
ADMISSION FILM
CASE B - JULY 28, 1928
INEFFECTIVE PNEUMOTHORAX
(ADHESION)
CASE B - FEB.6, 1929
EFFECTIVE PNEUMOTHORAX
AFTER PNEUMOLYSIS
CASE B - NOV. 27, 1929
MARKED SPREAD CONTRALATERAL SIDE
(PHRENISECTOMY)

FIG. 3

sis there was a severe reaction, the pulse rising to 110 and temperature to 102°. Roentgenograph a few days after the pneumolysis showed a complete collapse of the cavity and some fluid and adhesions at the base.

July, 1929: Patient has been free from symptoms and is now on thirty minutes' exercise. Recent physical and roentgenographic examinations show an almost complete reëxpansion of the lower lobe.

December, 1929: Slight cough and expectoration have developed; râles are present over the right lower lobe and over the upper part of the left lower lobe. Roentgenographs show a circumscribed area of infiltration in the upper portion of the left lower lobe.

April, 1930: A phrenicectomy has been done on the right side. Patient has remained free from symptoms and there has been a gain in weight; physical findings in left lung have increased; roentgenographs show that a cavity has been formed in the involved portion of the left lung.

The leucocytic graph of this case shows that when the study was begun in July, 1927, the leucocytic picture was septic in type. Following the institution of pneumothorax there was some change in the leucocytic picture, in that there was more of a tendency for the neutrophiles to come within normal limits; for the lymphocytes to remain above the lower limit of normal; and for the mononuclear leucocytes to remain within normal limits. That the pneumothorax was not satisfactory is shown by the neutrophiles being consistently above normal for three months before pneumolysis was done. Prior to pneumolysis there was also a marked decrease in lymphocytes, and a marked rise in mononuclear leucocytes. Subsequent to pneumolysis there was a sharp rise of lymphocytes which persisted for five months. During this period the neutrophiles and the mononuclear leucocytes showed a marked tendency to come within normal limits. From July, 1929, to date there has occurred a gradual change of the leucocytic reaction back to the type present at the beginning of the study. The graph shows that while the pneumothorax was beneficial it was not really effective until after pneumolysis, and that the failure of both the pneumolysis and the pneumothorax could be detected as early as July, 1929. With the active tuberculous process in the contralateral lung it is impossible to judge the effect of phrenicectomy in this case.

Case G.: Female, aged 20. *Past History:* Usual childhood diseases; influenza in 1919; bronchitis in 1924. *Present Illness:* In April, 1926, had a respiratory infection which was diagnosed as bronchitis; at this time there were cough, purulent expectoration, night-sweats, loss of weight; in June fever was present;

physical and roentgenographic examinations suggested pulmonary tuberculosis.

On admission to Sanatorium in July, 1926, patient presented cough, expectoration, fatigue, weight 20 per cent below normal, temperature range 98° to 100°, pulse-rate 70 to 100, sputum positive for tubercle bacilli (Gaffky VIII). There were physical signs over the left upper lobe and the upper part of the lower lobe. Roentgenograph showed a dense infiltration of the middle third of the left lung with cavitation.

March, 1927: Since admission there have been periods of clinical improvement followed by short periods of exacerbation. At such times the temperature has risen to 102° or higher, and the pulse-rate increased to 110. There has been a gain of 4.0 kg. in weight; physical findings are less; expectoration has been abundant and has shown tubercle bacilli on all examinations. Serial roentgenographs have shown a steady increase in size of the involved area. Pneumothorax was begun following one of the exacerbations.

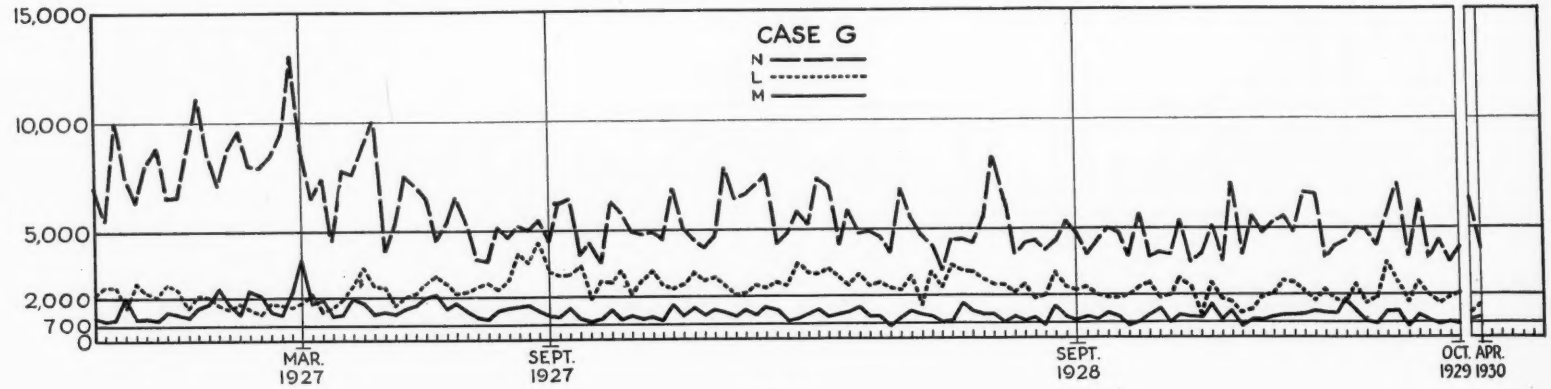
September, 1927: Symptoms have gradually subsided; expectoration has ceased; temperature has returned to normal; pulse-rate varies between 90 and 100; weight is less than on admission; râles persist; roentgenographs show a gradual collapse of the lung, adhesions at the base, and the presence of fluid.

September, 1928: During the past year clinical progress has been good; patient has gained 14.0 kg. in weight; temperature has remained normal; pulse-rate still above normal but less rapid than before; patient has been free from symptoms; recent physical examination showed the presence of râles at the base; roentgenograph showed a reëxpansion of the lung at the base due to adhesions.

October, 1929: There has been no change in the clinical condition of the patient. Physical signs are present over the lower half of the left chest; all efforts at further collapse were futile; a phrenicectomy was done, which resulted in a lowering of the pulse-rate; patient was discharged to continue her treatment at home.

April, 1930: Patient returned for examination. No change was found in the status of the pulmonary condition.

The leucocytic graph of this case shows beyond a question of doubt the beneficial effect of the pneumothorax. Before the pulmonary collapse was begun the leucocytic reaction indicated a progressive lesion. Following the pneumothorax a distinct change in the trend of the leucocytic reaction was noted, as shown by an increase of lymphocytes, a drop in the neutrophiles, and a slight tendency for the mononuclear leucocytes to recede. With the failure to keep the lung collapsed, due to "creeping" adhesions, the graph shows a distinct tendency for the leucocytic reaction to revert to the type present before treatment was begun. Phrenic-


CASE G
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L
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15,000
10,000
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MAR. 1927
SEPT. 1927
SEPT. 1928
OCT. 1929
APR. 1930

CHART 4

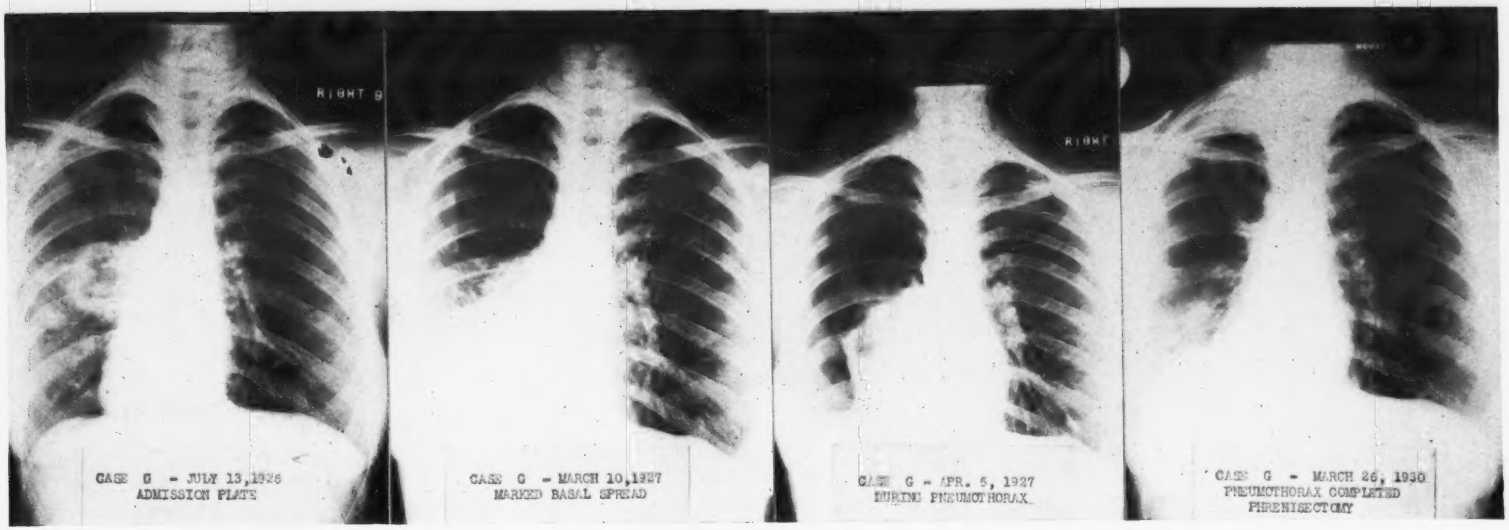
RIGHT G
CASE G - JULY 13,1926
ADMISSION PLATE
CASE G - MARCH 10,1927
MARKED BASAL SPREAD
RIGHT
CASE G - APR. 6, 1927
DURING PNEUMOTHORAX
CASE G - MARCH 26, 1930
PNEUMOTHORAX COMPLETED
PHRENISECTOMY

FIG. 4

ectomy does not appear to have helped the process. The pathological activity is not so severe now as before pneumothorax was started, but there is more evidence of a progressive than of a retrogressive process. This is shown by the tendency of the lymphocytes to drop below normal and the neutrophiles and mononuclear leucocytes to rise above normal.

Case St.: Female, aged 28. *Past History:* Chicken-pox, measles and pertussis during childhood. *Present Illness:* Noticed a loss of weight and was easily fatigued in December, 1926; in August, 1927, developed a "chest cold" with cough, expectoration, dry pleurisy and fever to 102°; at this time râles were present at both apices and tuberculosis was suspected; a diagnosis of pleurisy was made.

On admission to Sanatorium in October, 1927, the following findings were noted: cough, expectoration, sputum positive for tubercle bacilli (Gaffky II), night-sweats, pleurisy, temperature 98° to 100°, pulse-rate 90 to 100, weight 24 per cent below normal. There were physical signs over the left upper lobe and the upper portion of the lower lobe; no signs were noted in the right lung; roentgenograph showed a dense parenchymatous infiltration of the upper two-thirds of the left lung with a cavity present in the circle of the 2nd interspace.

November, 1927: Pneumothorax begun after one month of observation; satisfactory collapse was obtained after a few treatments; an adhesion at the level of the 2nd rib did not prevent collapse of the cavity; fluid was present.

January, 1928: Collapse is satisfactory; fluid is present and varies in amount from time to time; symptoms have disappeared; there is no expectoration; weight has increased 7.0 kg.; temperature is normal; pulse-rate varies between 80 and 100.

January, 1929: Patient has remained free from symptoms; weight has fluctuated but is now 9.0 kg. above admission weight; temperature and pulse have remained within normal; except for an occasional upper respiratory infection there has been no intercurrent illness; collapse of the lung is satisfactory; patient has been put on graded exercise.

November, 1929: Clinical picture has remained essentially the same; exercise has been increased; two years of satisfactory collapse have elapsed and collapse therapy has been discontinued.

April, 1930: Patient remains symptom-free; pulse and temperature remain normal; physical signs are absent; patient has gained 10.0 kg. since admission to Sanatorium; roentgenographs have shown a gradual reëxpansion of the lung without parenchymal changes in the reëxpanded portion; a small amount of fluid is still present.

The leucocytic graph demonstrates without comment the real benefit this case has received from the pneumothorax therapy. It remains to

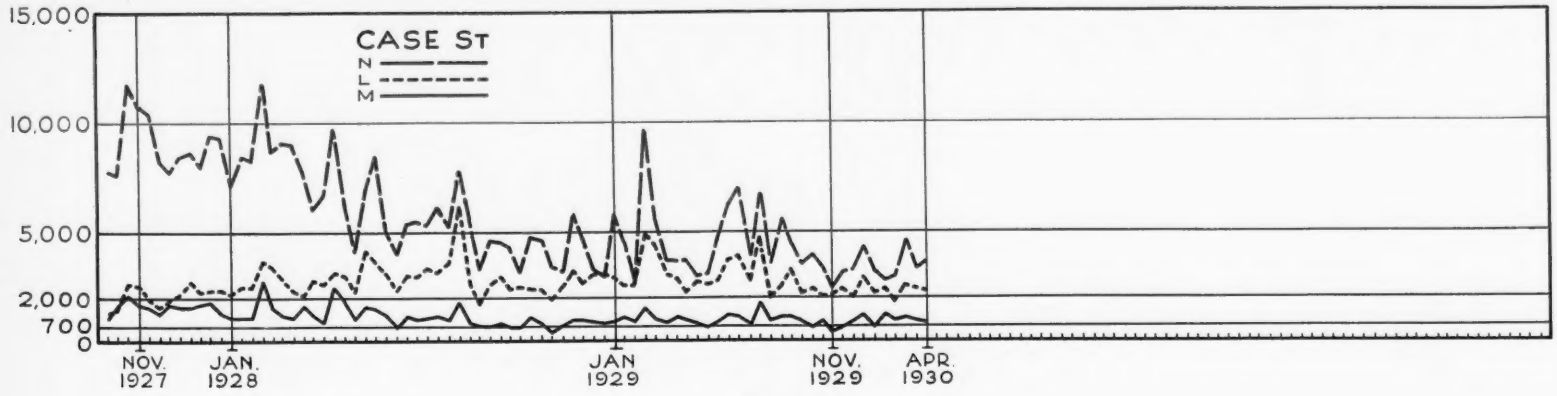
15,000
10,000
5,000
2,000
700
0
CASE ST
N
M
NOV. 1927
JAN. 1928
JAN 1929
NOV. 1929
APR. 1930

CHART 5

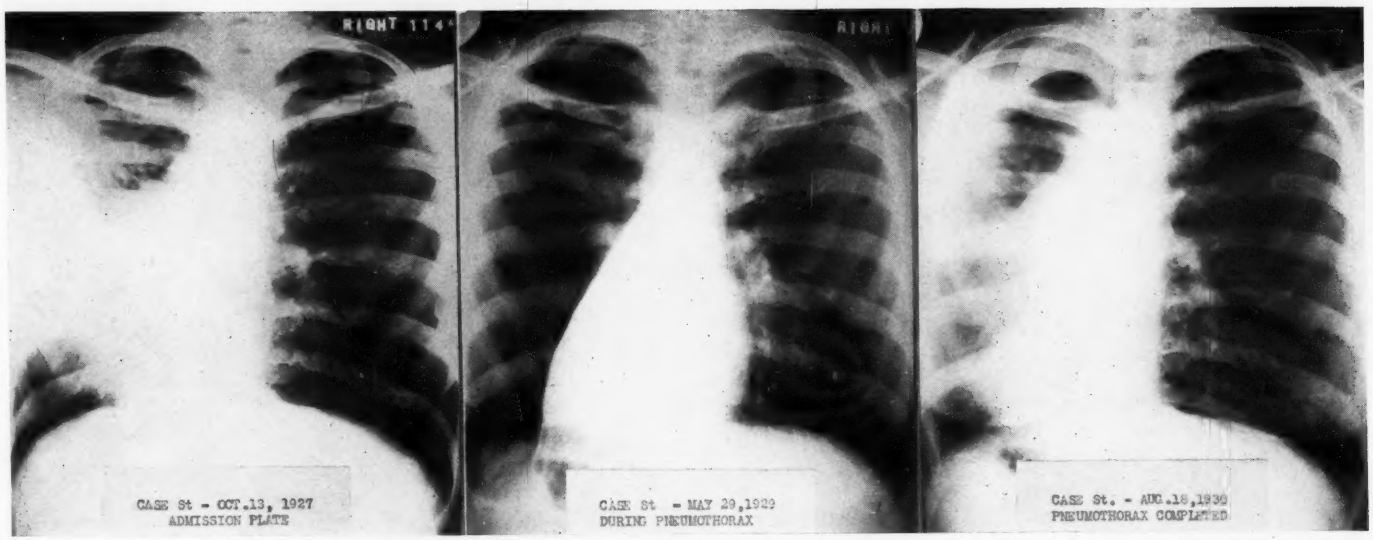
RIGHT 1174
CASE St - OCT.13, 1927
ADMISSION PLATE
RIGHT
CASE St - MAY 29,1929
DURING PNEUMOTHORAX
CASE St. - AUG.18,1930
PNEUMOTHORAX COMPLETED

FIG. 5

le determined, however, whether the collapse has been maintained long nough to establish an efficient cicatrization. The leucocytic reaction ignifies a healing stage of the tuberculous process, but from it one cannot ell that the process is permanently healed. By following the leucocytic eaction in such a case one will be able to detect a reactivation of the rocess if such should occur.

Case Sm.: Female, aged 21. *Past History:* Mumps, chicken-pox and measles in childhood; tonsillectomy at age 13; attacks of "grippe" in 1925 and 1926. *Present Illness:* Blood-streaked sputum in October, 1926; a frank haemoptysis two months later; from physical and roentgenographic findings a diagnosis of tuberculosis was made.

Patient admitted to Sanatorium in December, 1926; symptoms were cough, expectoration and fatigue; sputum was often blood-streaked and was positive for tubercle bacilli (Gaffky III); temperature normal; pulse-rate varied from 80 to 90; weight 8 per cent below normal; physical signs were present over the upper two-thirds of the left lung; roentgenograph showed parenchymatous infiltration of the upper third of the left lung.

April, 1927: Symptoms have persisted; an attack of pleurisy occurred in March; physical signs have remained; roentgenographs show an increase in the area of involvement; pulse and temperature have remained within normal; weight has increased to normal; pneumothorax was begun.

February, 1928: Patient has become symptom-free; expectoration is very slight and negative for tubercle bacilli; roentgenographs show a satisfactory collapse in spite of an adhesion at the apex; a small amount of fluid is present at the base; weight is now 5.0 kg. above normal; temperature and pulse have remained normal.

January, 1929: Clinical status of the case has remained satisfactory; a very satisfactory collapse has been maintained; graded exercises were begun six months ago.

June, 1929: A satisfactory collapse has been instituted for two years with excellent clinical progress; treatment has been discontinued and the lung allowed to reëxpand.

December, 1929: Patient has remained free from symptoms; on one occasion fine râles and a pleural rub were noted over the left chest posteriorly; lung has almost completely reëxpanded; fluid, which has been present throughout the treatment, has spread out over the lung surface; patient was discharged on full-time exercise with the request to return in six months for further examination.

June, 1930: Patient returned for examination. No evidence of an exacerbation of the tuberculous process was found.

From the clinical standpoint this case progressed under strict bed-rest treatment. Pneumothorax controlled the tuberculous process. The final result appears to be excellent.

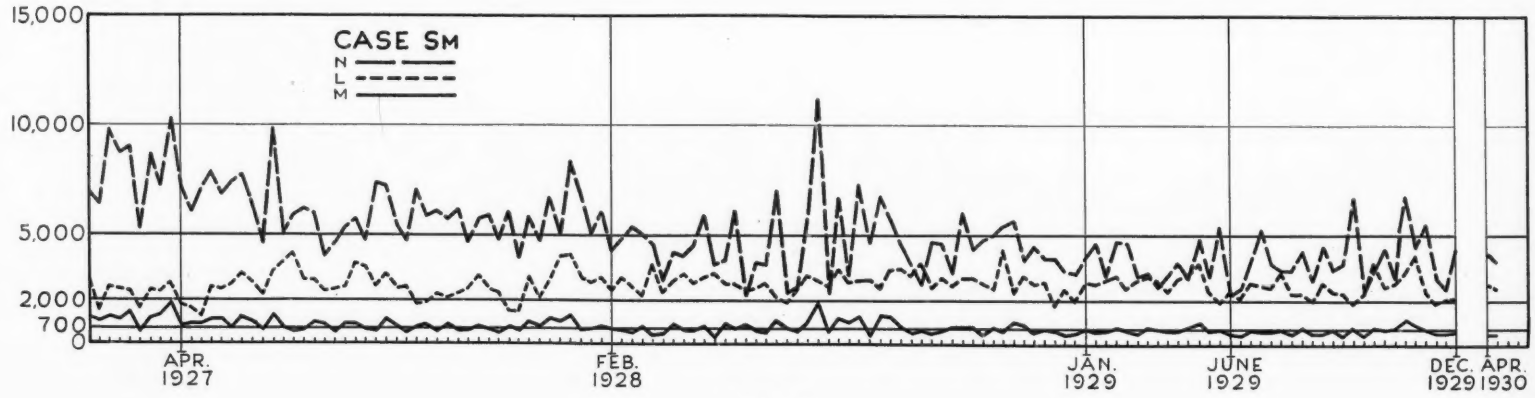
15,000
10,000
5,000
2,000
700
0
CASE SM
N
L
M
APR. 1927
FEB. 1928
JAN. 1929
JUNE 1929
DEC. 1929
APR. 1930

CHART 6

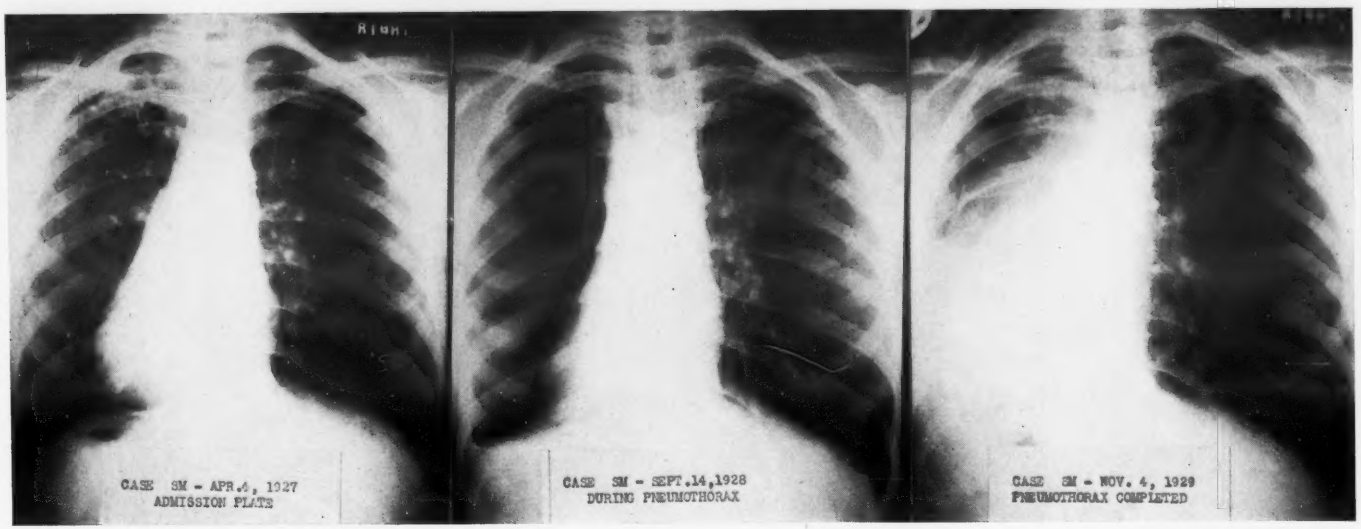
CASE SM - APR. 6, 1927
ADMISSION PLATE
CASE SM - SEPT. 14, 1928
DURING PNEUMOTHORAX
CASE SM - NOV. 4, 1929
PNEUMOTHORAX COMPLETED

FIG. 6

The leucocytic graph of this case shows the beneficial effect of the collapse therapy, although not so strikingly as it does in case St. At the beginning of the study there was a mild leucocytosis with the neutrophiles and the mononuclear leucocytes increased above the normal limits. The first change of significance after pneumothorax was instituted was a marked rise in the number of lymphocytes. During the first year of treatment the neutrophiles tended to remain above normal, the lymphocytes were usually increased, and the mononuclear leucocytes were more often above than within normal limits. During the last year of study the neutrophiles and the mononuclear leucocytes were generally within normal limits, while the lymphocytes were never decreased below the lower limits of normal and were quite frequently above the upper limits of normal. The high peak of neutrophiles in 1928 occurred shortly after the graded exercises were begun. A question which suggests itself is, was the compression as great as it should have been, for it took over a year to establish a good blood-count. It may be that the volume of damaged lung tissue was so great that it took that length of time for Nature to change it over to essentially a healing process and that greater compression would have done no further good.

DISCUSSION

The value of artificial pneumothorax as a therapeutic agent in the treatment of selected cases of pulmonary tuberculosis is now commonly accepted. There is, however, a considerable difference of opinion as to the type of case to be selected and the time when such treatment should be instituted, as well as the length of time it is necessary to keep the lung collapsed.

Failure of artificial pneumothorax to control the tuberculous process is common. The causes of such failures are multiple. Perhaps the most common cause is the presence of adhesions which prevent complete collapse of the diseased lung. To overcome the problem which adhesions present, phrenicectomy and pneumolysis have been evolved. At the present time there is no uniformity of opinion as to when such procedures should be used.

Another common cause of failure in pneumothorax is that the treatment is not begun until there has occurred a considerable involvement of the lung substance. The greater the involvement of the lung tissue the greater will be the difficulty of obtaining good compression, and the

longer will it take for the tuberculous area to be changed to a retrogressive and healing stage.

Up to the present time the success or the failure of collapse therapy has had to be judged entirely by roentgenographs and by the clinical progress of the case. It is commonly recognized that in tuberculosis the clinical improvement of a case is at times more apparent than real. This has been shown in some of our cases of pneumothorax. From the information we have gained from the leucocytic reaction in these cases we are of the belief that leucocyte counts should be used along with other data when an attempt is made to gain a comprehensive understanding of the actual status of a tuberculous case. The interpretation of the leucocyte count must rest in the hands of the physician in charge of the case. Such an interpretation should be made upon the basis of the pathology of the disease rather than upon the presence or absence of clinical symptoms. In any disease the final outcome depends more upon the underlying pathological condition than it does upon the presence or absence of apparent signs or symptoms. The more thoroughly the existing pathological condition is understood the more accurate will be the judgment of the physician relative to the *status quo* of his patient. For the clinician the nearest approach to the pathological status of tuberculosis is the leucocytic reaction. The leucocytic reaction is a valuable clinical adjunct. We are convinced that the information which a study of the leucocytes gives should be seriously considered even though the other clinical findings appear to contradict such information.

The literature on the leucocytic picture in tuberculous cases receiving collapse therapy is confined to a few reports from European investigators. Of these reports the one by Griesbach (3) is the most comprehensive, and, on the whole, is an excellent article. The following quotations from his report are in accord with our own observations:

> By holding to the right technic, the differential white blood picture in the hands of the expert is not only an indispensable, but the most important, adjunct of clinical examination methods in pulmonary tuberculosis . . . . The serial prosecution of hemogram forms or curves, which are naturally nonspecific for tuberculosis but absolutely pathognomonic, makes possible an accurate insight into the individual phases of the physical combat against infection, and permits us to establish the PROGNOSIS better than any other method of investigation. On this point the hemogram is far superior to the sedimentation reaction. . . . . The hemogram fulfills its most important function, in my opinion, by making possible the certain and quick recognition of the value

or worthlessness of any given treatment. . . . . The hemogram observations give weighty support for the indication of collapse therapy. . . . . The choice of the kind of collapse therapy can never be derived from the hemogram; it must be solely the result of clinical observations at the time.

Space prevents further excerpts from this excellent contribution.

All of the cases which we have studied began as uncomplicated cases of artificial pneumothorax. They were given pneumothorax because of the failure of the routine therapy commonly used in the treatment of tuberculosis cases. This failure has been evidenced by increased pulmonary involvement, as shown by physical examination and roentgenograph; or by increased symptoms, such as haemoptysis or increased pulse and temperature. During the course of our study complicating factors have entered in. Development of tuberculosis in the contralateral lung, spontaneous pneumothorax, and "creeping" adhesions have complicated the picture. Phrenicectomy and pneumolysis have been done in certain cases because the collapse therapy was not successfully controlling the tuberculous process. At first we considered reporting only on the successful uncomplicated cases of pneumothorax. On further consideration we decided to include all of the cases, since the complications encountered were those that might develop in any case which was given artificial pneumothorax. In other words, this report is not limited to successful cases of artificial pneumothorax. With the inclusion of all the cases one can better evaluate the factors that are essential for the success of the collapse therapy.

In a previous report one of us (4) has given the findings of a rather extensive study of the leucocytic reaction in tuberculous cases. The main conclusion of that report was that the leucocytic picture was often a more accurate index of the actual pathological status of the tuberculous lesion than were the other clinical findings. For the leucocytic reaction to be used it is necessary that the diagnosis of tuberculosis be established. The leucocytic picture cannot be used as a diagnostic means, since the leucocytic reaction is not specific for tuberculosis. After the diagnosis of tuberculosis is established it is essential that the leucocytic reaction be interpreted on the basis of the pathogenesis of tuberculosis, as reported by one of us (5). The relation of the circulating leucocytes to the pathogenesis of the tuberculous lesion may be briefly stated as follows: The mononuclear leucocyte (the monocyte of Sabin and others) represents tubercle-formation; the neutrophile represents the tubercle undergoing

abscess-formation; and the lymphocyte represents the healing phase of the tuberculous lesion.

In the graphs there are three horizontal lines to represent the normal limits of the three types of leucocyte in normal, healthy individuals (6). The upper line, at 5000, represents the upper limit of the neutrophile. In the tuberculous individual, when the neutrophiles are at or above this line one may correctly judge that the tuberculous process is undergoing abscess-formation. The middle line, at 2000, represents the lower limit of the lymphocyte. In an individual with tuberculosis, if the lymphocytes are at or below this line one may judge correctly that the tuberculous process is not healing. If they are consistently well above the line evidence is present that the tuberculous process is healing, at least in part. The lower line, at 700, represents the upper limit of the mononuclear leucocytes (monocytes). If these cells remain consistently above the line for several weeks one may conclude that new tubercles are being formed; that is, that the tuberculous process is "spreading." By taking into account the position of these three cell types in relation to their respective lines an accurate estimation of the status of the tuberculous process can be gained. This will apply in all cases and types of tuberculosis except those in which the total leucocyte count is below 7000. In such instances the differential percentages will have to be relied upon.

In our present study we have followed the leucocytic reaction, by weekly counts, for from one to three years, to determine what effect artificial pneumothorax might exert upon the leucocytic picture. We have found that the leucocytes reflect more accurately than do the other clinical findings the actual pathological status of the tuberculous process. Some cases which have shown clinical improvement have not shown an improvement in the leucocytic reaction, while in other cases improvement has occurred in both the leucocytic picture and in the clinical status. Subsequently, as shown in the cases cited above, the leucocytic reaction has been found to give the more correct information where there has been a disagreement with the other clinical data. We have not seen a single case in which the patient has become worse clinically and the leucocytes have indicated a real improvement at the time. This study has proved to us that a patient can harbor a serious tuberculous lesion, when judged from the angle of pathological change, at a time when the other clinical data suggest the reverse. Sooner or later the seriousness of the pathological process will make itself manifest.

CONCLUSIONS

1. Collapse therapy can be a very effective method of treatment in suitable cases of pulmonary tuberculosis. The success of such therapy depends upon instituting the treatment early and upon maintaining an effective collapse. An effective collapse is one which places under control the pathological process. This can be judged more accurately by a leucocytic graph than by any other single procedure.

2. Any case of pulmonary tuberculosis considered suitable for collapse therapy, which maintains a septic or a hyperplastic leucocytic picture consistently for two months under strict bed-rest therapy, should have the benefit of this treatment. Further delay, due to an apparent improvement of the case, may prove deleterious. The size of the lesion should not influence the decision.

3. If within six months after collapse therapy has been instituted the leucocytic picture does not show a trend toward improvement the collapse can be judged ineffective, if progressive tuberculosis in the contralateral lung or in other organs can be excluded. Additional methods, such as pneumolysis, phrenicectomy, and, last, thoracoplasty, should then be seriously considered.

4. The length of time necessary to hold a lung in effective collapse to ensure a satisfactory final result has not been established.

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CONCERNING THE DESENSITIZATION OF TUBERCULOUS GUINEA PIGS[1]

JOHN WEINZIRL AND RUBY M. BOHART[2]

In the laboratory sensitization to proteins is easily produced and desensitization readily accomplished. The sensitization of guinea pigs to egg-white is a familiar instance. After injecting a small dose of egg-white into a guinea pig, the animal becomes sensitive to this substance; if a second dose is injected a month later, then the animal develops anaphylactic shock, which frequently proves fatal. If, however, the animal survives the second dose, it is no longer sensitive for some days, when additional doses of egg-white may be injected without causing anaphylaxis. If a month or more is permitted to elapse after the second injection the guinea pig again becomes sensitive and reacts with anaphylactic shock to a subsequent dose.

Other instances similar to that of egg-white desensitization are well known. Persons subject to hay-fever are sensitive to some species of pollen; if an extract of the causative pollen is injected into the sensitized individual in suitable doses a few weeks previous to the pollen season, the person is partly or completely desensitized and may escape hay-fever. Children sensitive to horse-serum are subject to anaphylactic shock when antitoxin is administered. Anaphylaxis may be avoided by administering the antitoxin in small doses at short intervals, thereby causing desensitization.

It is doubtless unnecessary to cite other instances of desensitization. In general, proteins introduced parenterally into the body produce sensitization of one type or another, and small doses of the same protein subsequently introduced will cause desensitization. In tuberculosis a certain amount of sensitization is always present, as is shown by Koch's tuberculin reaction, by the Mantoux (1) intracutaneous test, and by the organic reaction of DeJong and Doorenbos (2). The question naturally

[1] Read at a session of the pathological section of the twenty-sixth annual meeting of the National Tuberculosis Association, Memphis, Tennessee, May 7–10, 1930.

[2] The Alice McDermott Foundation, University of Washington, Seattle, Washington.

arises, is it possible to desensitize in tuberculosis and thus avoid the adverse reaction? Could the reaction be eliminated by administering suitably sized doses of tuberculoprotein? If the principle of desensitization actually applies to tuberculosis, it would seem that the subject can be freed from one of the chief obstacles to immunization and recovery. The possibility seemed so alluring that we have devoted considerable time to its investigation. The chief object of the present study was to determine whether the sensitization of the skin, as manifested in tuberculous guinea pigs, could be reduced by administering suitable antigens.

REVIEW OF THE LITERATURE

In a previous paper one of us (3) has reported on the methods of inducing sensitization to the tubercle bacillus. This work showed that the typical sensitization accompanying the administration of living tubercle bacilli may also be obtained by means of killed tubercle bacilli. The results confirmed the work of Petroff and Stewart (4), who were able to sensitize by means of rather large doses of heat-killed tubercle bacilli. The work also showed that chemically-killed bacilli were considerably more potent in this respect than heat-killed bacilli. If the more effective sensitizer is also the more effective desensitizer, then this work seemed to open greater possibilities for desensitization.

A careful search of the literature failed to reveal any contributions approaching the problem of tuberculosis from the point of view of desensitization. Although many workers have administered tuberculins and killed tubercle bacilli to tuberculous subjects, it would be futile to review this literature, since their immediate objects were different from ours. It is sufficient to say that good results were obtained at times, but these could not be reproduced at will.

One investigation, while made for another purpose, is so interesting and the desensitization effect is so clear that it should be included here. The work of Krause and Willis (5) has been an inspiration to us. They inoculated guinea pigs with living tubercle bacilli. After tuberculosis was established they inoculated daily doses of living tubercle bacilli into these tuberculous animals and made skin tests and other observations. They were surprised to see the skin reaction practically disappear, and were so impressed with the results that they published them in beautifully colored plates. They were also surprised that the animals withstood these daily doses so well and that they were in relatively good physical condition at the close of the experiment. On autopsy, the disease was less marked in the experimental animals than in the controls. The fact that their method did not lead to the arrest of the disease does not negative the fundamental significance of their work. If we assume that Krause and Willis really obtained desensitization, then the results are in accord with our theory.

Since this paper was written there has appeared another contribution which bears directly upon our topic; the work of Rich and McCordock (6) discusses the rôle of allergy and other factors in relation to the pathogenesis of tuberculosis; hence it is much broader than the question confronting us. They do state, however, that "it is our belief that any beneficial effect which may follow treatment with tuberculin is less referable to perifocal inflammation than to desensitization and will occur only in those cases in which desensitization of a proper degree has been accomplished." Later they state "We have, ourselves, as yet no experimental proof of the beneficial effect of complete desensitization, but one of us is engaged at present in such experiments." They also quote from Hamman and Wolman's book, *Tuberculin in Diagnosis and Treatment:* "In the majority of cases such a change for the better is associated with the development of a tolerance for tuberculin. This is a clinical fact, whatever our theories may be." They distinguish clearly between allergy and immunity as separate phenomena. Earlier they state that their "conclusions are based upon the results of the experimental infection of about a thousand animals. . . . and two hundred autopsies on cases of human tuberculosis." In this contribution of 150 pages the authors have definitely approached the problem of desensitization, and their experimental results will be awaited with great interest.

PLAN OF WORK

Obviously it was desirable to carry out our experiments on suitable animals and for this purpose the guinea pig appeared satisfactory. We already knew that this animal could be readily sensitized by administering living or killed tubercle bacilli. To desensitize we decided to use bacillary products such as bouillon filtrate, tuberculin, and proteins precipitated from them, and also bacilli killed in various ways. Specifically, it was necessary to determine: (a) the most appropriate dose of antigen to be employed; and (b) the best interval to use in administering the desensitizing dose. Suitable protocols were planned, varying first one, then the other of these two factors. The results were checked by the skin test of Mantoux (intracutaneous).

RESULTS OBTAINED

From the work on sensitization in tuberculosis, we knew that the tuberculins were less effective sensitizers than the bacillary bodies; still this did not determine which were the most satisfactory desensitizers. Accordingly, we tried Old Tuberculin (O. T.), then the broth filtrate, (B. F.), from which O. T. is prepared, and finally the protein precipitated

from the filtrate. Then we employed dead bacillary bodies in a number of forms, such as iodine-killed, carbol-fuchsin-killed, and ether-killed tubercle bacilli. Of necessity, the three phases of the problem, (a) most suitable antigen for desensitization, (b) size of dose and (c) spacing of the doses, could not be separated from one another but had to be combined in each protocol. While our chief concern was to find the most suitable antigen, we were obliged to consider the other two factors at the same time. Each protocol, therefore, involves the three problems. A considerable number of protocols were carried through, but only representative ones will be given, such as contributed materially to the solution of one or more of the questions confronting us.

Desensitization of Tuberculous Guinea Pigs by means of Dialyzed Long's Medium-Filtrate: Our first attempt at desensitization of tuberculous guinea pigs was by means of the dialyzed Long's medium-filtrate. Eight animals were rendered tuberculous by intraperitoneal inoculation with *Mycobacterium tuberculosis*, strain 1701, a culture received from the Michigan State Department of Health, and said to be H37. The sensitizing dose was 0.01 mgm. The animals were first tested for sensitization on the fifteenth day by means of a 5 per cent solution of O.T., 0.1 cc. being injected intracutaneously. Most of the animals gave a four-plus reaction.

Forty-one days after inoculation desensitization was begun by administering Long's medium-filtrate prepared in the laboratory. Human strain 1702, received from the Michigan State Department of Health, where it was isolated, was grown on Long's synthetic medium for four months, filtered through paper, and the filtrate dialyzed in collodion sacs to remove salts which cause disagreeable symptoms when administered intraperitoneally. The filtrate was then placed in petri dishes and rayed for 35 minutes with a mercury-arc lamp at a distance of six inches to kill living bacilli present. The desensitizing dose was varied in amount and was given in six subdoses at one-half-hour intervals, after the manner of desensitization in cases of serum sensitization. The desensitization was repeated at 7-day intervals. Skin tests were also made at 7-day intervals, with each test falling three days previous to administering the filtrate. The results are recorded in protocol 1.

The results recorded in protocol 1 show a change in the skin reaction in that necrosis was absent or greatly decreased and the systemic reaction was markedly diminished. By systemic reaction is meant the limp condition characteristic of a tuberculous animal following the adminis-

tration of a dose of tuberculin. While the skin tests were made at stated intervals, four days after each dosing, most of them are omitted since they do not show any marked change from the earlier results. Later it became apparent that these tests were made too soon after administering the desensitizing dose. A seven- or ten-day test might have given better results.

PROTOCOL 1

Desensitization of tuberculous guinea pigs by means of dialyzed Long's medium-filtrate

	DAY	TEST ANIMALS						TUBERCULOUS CONTROLS	
Guinea pig number		264	265	276	277	278	279	266	267
Living H37 (mgm.)	1	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Skin test	40	4+	4+	6+	6+	6+	6+	4+	4+
Weight (gm.)	40	470	450	455	500	444	344	355	440
Filtrate (cc.)	40	0.006	0.006	0.06	0.06	0.3	0.3	0	0
Skin test	42	2+	3+	2+	2+	Dead	3+	4+	4+
Skin test	49	1+	4+	3+	2+		6+	8+	4+
Filtrate (cc.)	50	0.006	0.006	0.06	0.06		0.3	0	0
Filtrate (cc.)	57	0.006	0.006	0.06	0.06		0.6	0	0
Filtrate (cc.)	64	0.006	0.006	0.06	0.06		0.6	0	0
Filtrate (cc.)	71	0.006	0.006	0.6	0.6		0.6	0	0
Filtrate (cc.)	79	0.006	0.006	0.06	0.06		0.6	0	0
Filtrate (cc.)	86	0.06	0.06	0.6	0.6		1.0	0	0
Skin test	100	3+	4+	2+	3+		3+	10+	6+
Filtrate (cc.)	103	0.06	0.06	0.6	0.6		1.0	0	0
Filtrate (cc.)	110	0.06	0.06	0.6	0.6		1.0	0	0
Skin test	114	3+	3+	0	4+		4+	6+	10+
Filtrate (cc.)	117	0.6	0.6	0.9	0.9		1.2	0	0
Skin test	121	4+	4+	0	4+		4+	6+	4+
Skin test	128	3+	4+	4+	3+		4+	10+	10+
Filtrate (cc.)	149	0.6	0.6	Dead	0.9		1.2	0	0
Filtrate (cc.)	156	0.6	0.6		0.9		2.0	0	0
Filtrate (cc.)	188	0.6	0.6		0.9		2.0	0	0
Filtrate (cc.)	202	0.5	0.5		0.8		1.5	0	0
Skin test	209	6+	6+		4+		Dead	6+	8+
Weight (gm.)	212	540	500		585		460*	475	570

*At death.

The dose of antigen was increased tenfold on the 86th day, and 100-fold on the 117th day. Increasing the dose did not give increased desensitization according to the skin test, but the reaction was slower in developing. The systemic reaction was decreased, the larger doses being borne better than the smaller ones. At the beginning of the desensitizing process, guinea pig 278 was killed by 0.3 cc. of the antigen, but after

several desensitizing doses animal 279 was finally able to withstand 2.0 cc. without showing the characteristic collapse. On autopsy, the controls showed advanced tuberculosis, while the treated animals, with the exception of no. 278, revealed only slight tuberculosis.

A second trial with Long's medium-filtrate was made. Ten light-colored female guinea pigs were used, eight being rendered tuberculous by the intracutaneous injection of 0.2 mgm. of living tubercle bacilli, H37. After 23 days they were given a skin test and all developed a four-plus reaction.

Desensitization was attempted by means of dialyzed Long's medium-

PROTOCOL 2

Desensitization of tuberculous guinea pigs by means of dialyzed Long's medium-filtrate

	DAY	TEST ANIMALS TREATED								TUBERCULOUS CONTROLS	
		Intraperitoneally			Subcutaneously			Intracutaneously			
Guinea pig number....		563	564	567	568	534	578	570	571	616	617
Living H37 (mgm.).....	1	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Skin test.....	23	4+	4+	4+	6+	4+	8+	4+	4+	4+	4+
Weight (gm.).....	23	630	545	585	510	535	570	555	650	530	460
Filtrate (cc.).....	27	0.6	0.6	0.3	0.3	0.6	0.6	0.6	0.6	0	0
Filtrate (cc.).....	34	0.5	0.5	1.0	1.0	1.5	1.5	0.5	0.5	0	0
Skin test.....	38	4+	4+	0	4+	4+	3+	4+	4+	10+	4+
Filtrate (cc.).....	48	0.5	0.5	1.0	1.0	1.5	1.5	0.5	0.5	0	0
Skin test.....	52	6+	6+	3+	2+	4+	10+	10+	4+	10+	6+
Filtrate (cc.).....	72	0.5	0.5	1.0	1.0	1.5	1.5	0.5	0.5	0	0
Skin test.....	76	4+	6+	Dead	Dead	1+	Dead	Dead	2+	10+	10+
Filtrate (cc.).....	102	0.5	0.5			1.5			0.5	Dead	Dead
Skin test.....	106	3+	6+			2+			6+		
Skin test.....	148	Dead	Dead			3+			6+		
Weight (gm.).....	150					645			515		

filtrate from strain 1702. The product was rayed with mercury-arc light to kill any tubercle bacilli included. The dose of filtrate was divided into six subdoses which were administered at 30-minute intervals. The test varied from the first in that the dose was increased, and the inoculation for sensitization was made intracutaneously instead of subcutaneously. The results are given in protocol 2.

The results recorded in protocol 2 show considerable desensitization, as indicated by the skin test. The two controls gave high results ending with a 10+, while the animals under test generally gave lower results, usually near a 4+, but occasionally as low as a 2+ or 1+.

The desensitizing dose given on the 72nd day proved to be too large when four of the animals succumbed, and the rest were badly prostrated. The animals that survived outlived the controls. On autopsy only moderate tuberculosis was present, while the controls died with advanced tuberculosis.

Summarizing the results from the two trials with Long's medium-filtrate, we find that considerable desensitization was obtained and the systemic reaction was reduced. The greatest difficulty encountered was the high toxicity of the filtrate.

Desensitization of Tuberculous Guinea Pigs by means of Tuberculoprotein: The tuberculoprotein was obtained from Long's medium-filtrate by first dialyzing to remove salts, then precipitating the protein with

PROTOCOL 3

Desensitization of tuberculous guinea pigs by means of tuberculoprotein

	DAY	TEST ANIMALS			
Guinea pig number		17	18	19	20
Living 1702 (mgm.)	1	0.1	0.1	0.1	0.1
Skin test	20	4+	4+	4+	4+
Skin test	134	8+	6+	6+	6+
Protein 115 (cc.)	136	1.0	1.0	1.0	1.0
Skin test	143	4+	2+	4+	4+
Skin test	149	1+	1+	1+	0
Skin test	167	4+	4+	4+	3+

three volumes of acetone to one of filtrate. The precipitate obtained was filtered out, redissolved in an equal volume of normal salt solution and centrifugated to remove any tubercle bacilli that might be present. Thymol was added to ensure sterility. This solution was then used for desensitization purposes.

In our first trial with tuberculoprotein four guinea pigs were used. The animals were rendered tuberculous by injecting intracutaneously 0.1 cc. of a gelatin culture of a virulent strain of tubercle bacilli, 1702. On the 20th day the skin test gave a 4+ for all the animals. Desensitization was delayed to the 136th day, when the animals were given the acetone-insoluble protein from tubercle bacillus 115, a virulent strain grown on Long's medium. The precipitate from 100 cc. of filtrate was redissolved in 10 cc. of normal salt solution, and this solution was used for desensitization. The results are given in protocol 3.

Protocol 3 shows that the method of inoculation was successful in producing a high degree of sensitization. A skin test two days after administering the tuberculoprotein was still high, but it had nearly disappeared after twelve days. Later the reaction returned to a 4+. The number of animals involved was too limited to make the protocol significant, but it seems to indicate that tuberculoprotein can desensitize, and that the sensitization returns after a period of incubation.

In our second trial with tuberculoprotein eight light-colored guinea pigs were employed. Six of these animals were rendered tuberculous by intra-

PROTOCOL 4

Desensitization of tuberculous guinea pigs by means of water-soluble tuberculoprotein

	DAY	TEST ANIMALS					TUBERCULOUS CONTROL
Guinea pig number		81	83	84	256	259	435
Living H37 (mgm.)	1	2.0	2.0	2.0	1.5	1.5	1.5
Weight (gm.)	42	477	491	610	390	353	450
Skin test	42	6+	10+	10+			
Protein (cc.)	45	5	0.65	2.0			
Skin test	49	4+	6+	0			
Protein (cc.)	55	3.2	3.2	3.2	6.2	6.4	
Skin test	58	0	4+	4+			
Skin test	79	4+	4+	1+			
Protein (cc.)	90	3.15	3.15	3.15	6.35	3.15	
Skin test	93	Dead	2+	1+	6+	4+	4+
Protein (cc.)	96		5.6	5.6	3.15	3.15	
Skin test	99		1+	0	8+	Dead	4+
Skin test	113		1+	Dead	4+		4+
Skin test	127		1+		3+		6+
Skin test	155		4+		4+		6+
Protein (cc.)	159		1.9		0.7		
Skin test	162		4+		Dead		4+
Weight (gm.)	170		555				675

peritoneal injections of 1.5 and 2.0 mgm. of living H37 and two served as normal controls. After 42 days the skin reaction was a 4+ or more. The tuberculoprotein was derived from the filtrates from three strains of tubercle bacilli, and was administered subcutaneously. The results are recorded in protocol 4.

The results given in protocol 4 show some lowering of the skin reaction after the administration of the protein. At no time did the normal controls show a positive skin test; hence the results are omitted from the record. The character of the reaction was changed, the inflammation

disappearing sooner than on the tuberculous control. On the whole the trial confirmed the earlier result as to the value of tuberculoprotein for desensitization purposes.

In a third trial with tuberculoprotein eight light-colored female guinea pigs were used. They were rendered tuberculous by means of 1.5 mgm. of living bacilli, H37, injected intraperitoneally. After 12 days all showed a 4+ or more. Desensitization was attempted by means of two tuberculoproteins, one derived from a virulent strain, 1703, grown on potato-infusion broth, the other from an avirulent strain, KI, grown on Long's medium. The results are recorded in protocol 5.

The results given in protocol 5 were surprising in that the protein from

PROTOCOL 5

Desensitization of tuberculous guinea pigs by means of tuberculoprotein

	DAY	TEST ANIMALS RECEIVED							TUBERCULOUS CONTROL
		1703 protein			KI protein				
Guinea pig number		253	254	255	256	258	259	260	435
Living H37 (mgm.)	1	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Weight (gm.)	12	414	415	476	350	359	365	360	
Skin test	15	6+	6+	6+	4+	4+	4+	4+	4+
Protein (cc.)	17	7.5	7.5	6.2	6.2	6.2	6.4	6.4	0
Skin test	20	0	1+	0	Dead	Dead	3+	Dead	4+
Skin test	27	1+	1+	3+			3+		6+
Protein (cc.)	33	3.15	6.3	3.15			6.4		0
Skin test	36	0	Dead	4+			4+		4+
Protein (cc.)	55	Dead		3.15			3.15		0
Skin test	88			4+			Dead		6+

the avirulent culture, KI, proved to be the more toxic of the two, and killed 3 of the 4 guinea pigs with the first desensitizing dose. In the case of strain 1703, grown on potato bouillon, the bacillary protein was diluted by several times its volume of potato protein, which may account for its lower toxicity. The surviving animals showed a quite decided lowering of the skin reaction, and the systemic reaction was greatly reduced. The trial indicates that desensitization with tuberculoprotein is possible, but that it is accompanied with a risk due to the high toxicity of the product.

Summarizing the results obtained with the tuberculoprotein precipitated from Long's medium-filtrate, it appears that a considerable degree of desensitization was secured. While the skin reaction was not entirely

lost, it was materially reduced as compared with the control reactions. The systemic reaction was greatly diminished.

One reason for the uncertain results obtained in the trials with tuberculoprotein may be found in the spacing of the doses. We learned later that the best results are obtained when the antigen is given regularly at seven-day intervals. In these protocols the interval was irregular and frequently sufficiently long to permit resensitization to occur.

PROTOCOL 6

Desensitization of tuberculous guinea pigs by means of tubercle bacilli killed by carbol-fuchsin

	DAY	TEST ANIMALS						TUBERCULOUS CONTROLS	
Guinea pig number		520	517	518	519	514	523	525	533
Living H37 (mgm.)	1	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Weight (gm.)	59	Dead	512	510	340	465	Dead	403	Dead
Skin test	59		6+	6+	6+	10+		4+	
Killed bacilli:									
(a) Total dose (mgm.)	59		10	10	10	10			
(b) Number of subdoses			4	2	1	1		Dead	
c) Time-interval (days)			5	10					
Skin test	67		4+	4+	Dead	Dead			
Killed bacilli:									
(a) Total dose (mgm.)			10	10					
(b) Number of subdoses			3	2					
Skin test	82		3+	2+					
Killed Bacilli:									
(a) Total dose (mgm.)			10	10					
(b) Number of subdoses			3	1					
Weight (gm.)	108		520	630					
Killed Bacilli:									
(a) Total dose (mgm.)			10						
(b) Number of subdoses			1						
Skin test	110		3+	2+					
Skin test	124		4+	2+					
Killed Bacilli:									
(a) Total dose (mgm.)			10						
(b) Number of subdoses			4						
Skin test	163		3+	3+					
Weight (gm.)	163		420	750					

A distinct disadvantage in the use of the acetone-insoluble fraction of tuberculoprotein is its high toxicity. Doubtless the sensitization in tuberculosis is due to all of the proteins in the bacillus and is not limited to the highly toxic fraction. If the less toxic proteins were employed for desensitization, larger doses might be given with presumably greater desensitization.

Desensitization of Tuberculous Guinea Pigs by means of Tubercle Bacilli Killed by Carbol-Fuchsin: In the first trial with bacilli killed by carbol-fuchsin eight guinea pigs were used, two serving as controls. They were all rendered tuberculous by subcutaneous inoculation of 0.5 mgm. of living H37. On the 59th day the skin test gave a 4+ or better reaction. They were given a desensitizing dose of 10 mgm. of bacilli, strain 1702, killed by carbol-fuchsin. The results are given in protocol 6.

The results of this trial were disappointing because of the loss of three animals before desensitization began. Obviously desensitization was delayed too long. However, the test was continued to see what desensitization might accomplish in advanced tuberculosis. The first desensitization trial killed two more animals and the other two gave a decreased

PROTOCOL 7

Desensitization of tuberculous guinea pigs by means of tubercle bacilli killed by carbol-fuchsin

	DAY	TEST ANIMALS						TUBERCULOUS CONTROLS	
Guinea pig number		288	291	296	299	502	503	526	527
Living H37 (mgm.)	1	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Weight (gm.)	55	555	465	565	590	383	345	430	415
Killed bacilli:									
(a) Total dose (mgm.)	55	2	2	2	2	2	2	0	0
(b) Number of subdoses		5	5	5	5	5	5		
(c) Interval (hrs.)		8	8	24	24	72	72		
Skin test	60	Dead	0	6+	6+	Dead	Dead	4+	6+
Skin test	80		Dead	4+	4+			6+	4+
Skin test	96			10+	10+			10+	Dead

skin reaction, but it was still high, being 4+. These two animals were given four subsequent treatments, and skin tests were made which showed that skin desensitization could be decreased but not obliterated. The remarkable point in this trial was the decrease in the systemic reaction, the two animals standing the later treatments with very little discomfort. The animals were killed on the 163rd day to terminate the experiment. They had outlived the controls by more than three months and were in excellent physical condition.

A second trial was undertaken, using bacilli killed by carbol-fuchsin for desensitization. The conditions virtually repeated those of the former protocol, only the time-interval in spacing the dosage being changed from 5, 10 and 15 days to 1/3, 1 and 3 days. The results are recorded in protocol 7.

The protocol shows results essentially similar to those of the former. The first desensitizing dose killed half of the animals. Another animal died soon after, leaving only two for the continuation of the trial. The animals did not show any evident decrease in the skin reaction, but the systemic reaction was noticeably lessened.

Summarizing the results with bacilli killed by carbol-fuchsin, we found the antigen too toxic for use in advanced tuberculosis. Obviously the the size of the dose, 10 mgm., was too large. In a general way it would appear that the eight-hour spacing was unfavorable, as the doses seemed to coalesce and give the effect of a single large dose; 15-day spacing was unfavorable because the sensitization began to return. While the trials with the antigen killed by carbol-fuchsin are obviously inadequate, we

PROTOCOL 8

Desensitization of tuberculous guinea pigs by means of tubercle bacilli killed by ether

	DAY	TEST ANIMALS						TUBERCULOUS CONTROLS	
Guinea pig number		289	290	294	295	297	298	500	501
Living H37 (mgm.)	1	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Weight (gm.)	55	525	500	515	492	570	495	470	492
Skin test	55	10+	10+	10+	10+	10+	10+	10+	10+
Killed bacilli:									
(a) Total dose (mgm.)	55	2	2	2	2	2	2		
(b) Number of subdoses		5	5	5	5	2	2		
(c) Time-interval (hrs.)		8	8	24	24	72	72		
Skin test	60	10+	4+	0	Dead	6+	4+	6+	6+
Skin test	70	6+	4+	1+		4+	4+	6+	10+
Skin test	75	6+	6+	Dead		4+	4+	10+	10+

did not feel inclined to set up more protocols with it since other antigens seemed more promising.

Desensitization of Tuberculous Guinea Pigs by means of Bacilli Killed by Ether: In the first trial with ether-killed bacilli, eight guinea pigs were employed. These animals had previously received three doses of Long's medium-filtrate rayed with the mercury-arc lamp, but had failed to sensitize. They were inoculated intraperitoneally with 0.5 mgm. living H37, and on the 55th day all gave a 10+ skin reaction. They were then given desensitizing doses of ether-killed bacilli, 1703, a virulent human strain. The antigen was prepared by keeping it under ether for 30 days and shaking it daily. The ether was decanted to remove in part the soluble fats and proteins, the residue was then dried, and later it was

suspended in normal salt solution for injection. The results are given in protocol 8.

Although the animals had advanced tuberculosis when desensitization was begun, the protocol shows that only one animal was killed during the first desensitizing process. The antigen was probably less toxic than the carbol-fuchsin-killed bacilli. In the treatment of the bacilli with ether some of the highly toxic water-soluble protein is eliminated. There is some indication in the skin test that the animals were partially desensitized. The reactions were generally less than with the controls and they also differed in character. Four more treatments, not shown in the protocol, were given to the remaining animals, but without producing

PROTOCOL 9

Desensitization of tuberculous guinea pigs by means of bacilli killed by ether

	DAY	TEST ANIMALS						TUBERCULOUS CONTROLS		
Guinea pig number		280	281	292	512	282	283	510	511	293
Living H37 (mgm.)	1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Skin test	24	4+	6+	4+	6+	10+	6+	6+	6+	6+
Skin test	58	4+	10+	10+	10+	6+	6+	10+	10+	10+
Weight (gm.)	58	610	555	510	680	640	600	580	475	632
Killed bacilli (mgm.)	62	10	10	10	10	10	10	0	0	0
Time-interval (days)		5	5	10	10	3	3	—	—	—
Skin test	66	3+	6+	4+	4+	4+	4+	10+	10+	6+
Killed bacilli (mgm.)	70	3	3	1	Dead	5	5	0	0	0
Skin test	80	0	4+	4+		3+	3+	10+	10+	6+
Killed bacilli (mgm.)	84	30	30	10		40	40	0	0	0
Skin test	94	4+	4+	4+		4+	1+	6+	6+	10+

any material change in the skin test. The systemic reaction was much less severe. Numbers 290 and 297 outlived the controls.

In the second trial with bacilli killed by ether nine guinea pigs were used. These animals had received previously a one-milligram dose of killed tubercle bacilli intracutaneously, but had failed to become satisfactorily sensitized. They were then inoculated intracutaneously with 0.1 mgm. of living bacilli, H37. All gave a 4+ skin test on the 24th day. On the 58th day the skin reaction had either remained constant or had increased. Desensitization was begun on the 62nd day by injecting intraperitoneally 10-mgm. doses of bacilli, 1703, killed by ether. Desensitization was repeated at intervals and skin tests made periodically. The first two treatments only are included in protocol 9.

The results shown in protocol 9 indicate a considerable decrease in the skin reaction. The animals were not prostrated by the second treatment as they usually are with tuberculin or its equivalent, that is, the systemic reaction was practically absent. The autopsies showed that massive doses of killed bacilli injected intraperitoneally produced extensive adhesions, due doubtless to the fats contained in the bacilli.

Summarizing the results obtained with the bacilli killed and treated with ether, we find that the skin test shows some desensitization while the systemic reaction indicates marked desensitization. The chief difference between this and the other antigens tested consisted in the lessened toxicity of this antigen.

DISCUSSION

The protocols recorded above fall far short of our present ideals, but they have been deemed worthy of publication partly because they present a somewhat different approach to the problem of tuberculosis, and partly as notice to others of mistakes that may be avoided. We feel, however, that rather than repeat the protocols in more ideal form, we will use the systemic reaction instead of the skin test as the basis for future work.

At the beginning of this investigation certain definite questions presented themselves for solution: (a) Is it possible to desensitize tuberculous guinea pigs? (b) If desensitization is possible, what is the best antigen for this purpose? (c) What should be the size of the dose? (d) How should the doses be spaced to give the best results? The foregoing protocols afford answers to some of these questions and provisional answers to others.

As to the possibility of desensitizing tuberculous guinea pigs, the answer appears to be that partial desensitization is possible. However, the skin test probably fails to give a true picture of what happens in the body generally. Since skin tests with O.T. are so easily made and have come to be so widely employed, we were partially misled in giving too great a value to skin sensitization. This test is so sensitive that it indicates exceedingly slight degrees of sensitization which, however, may not greatly hinder recovery. On the other hand, the work definitely showed that the systemic reaction ("organic" reaction of De Jong and Doorenbos) can be largely, if not entirely eliminated. We are now investigating this phase of the problem more specifically.

Regarding the best antigen, we are perhaps only at the threshold of a satisfactory answer. We have reported on only four antigens, as

follows: (a) tuberculin, (b) tuberculoprotein, (c) carbol-fuchsin-killed bacilli, and (d) ether-killed and treated bacilli. It may be that any of these antigens can be successfully employed. It would seem, however, that the least toxic antigen that will still desensitize is the one to choose. The present trials seem to indicate that the ether-killed and treated antigen is the most suitable. The treatment with ether removes part of the lipoids which cause fibrosis, and also the more toxic proteins of the tubercle bacillus, but it still leaves proteins suitable for desensitization. The other antigens retain more of these objectionable constituents. On the basis of present data, we favor the ether-treated antigen for desensitization.

Concerning the size of the desensitizing dose no exact figures can be given because it must vary with the antigen employed. However, a general answer is indicated by the trials. The dose of antigen should fall below the amount that will arouse a violent reaction.

Time-interval between dosing is determined by two factors, namely: (a) the time required for the absorption of the protein injected; and (b) the time of reappearance of sensitization. If the time-interval is too short for the protein to be absorbed, the doses tend to coalesce and give the effect of a single large one, thus producing a violent reaction; on the other hand, if the time-interval is too long, sensitization reappears, and the desensitization is largely or wholly lost. In general, a time-interval of less than five or more than ten days is undesirable. We have adopted an average figure of seven days as most suitable.

The greatest obstacle encountered during the present work was the high toxicity of the antigens employed. If the dose was increased a limit was soon reached at which the animals were killed outright. This toxicity we assumed to be due to the proteins, 304 and 903, isolated by Johnson and studied by Sabin and Doan (7). Later results as reported by White (8) indicate that a toxic carbohydrate is present in these proteins, and that it may be removed by hydrolysis. If the tubercle proteins can be detoxified without denaturing them, then another possibility is opened for more successful desensitization. Work along this line is under way.

SUMMARY AND CONCLUSIONS

1. Protocols were carried out testing the value for desensitization purposes of (a) dialyzed Long's medium-filtrate; (b) tuberculoproteins

derived from Long's medium-filtrate; (c) tubercle bacilli killed by carbol-fuchsin; and (d) tubercle bacilli killed and treated with ether.

2. These trials show that desensitization, as indicated by the skin test, is only partially successful, but the reaction is frequently reduced below a 4+. If, however, the systemic reaction is considered, then desensitization seems to be more complete. Desensitization largely eliminates the prostration following the administration of tuberculoantigens.

3. Of the antigens tested, the ether-killed and treated tubercle bacilli seemed to give the most satisfactory results.

4. The size of the dose must vary with the antigen employed. It should be kept sufficiently low to avoid a violent systemic reaction.

5. The dosing should be spaced so as to avoid (a) coalescing of the doses and (b) the return of sensitization. Less than five or more than ten days are undesirable.

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THE THEORY OF THE MECHANISM UNDERLYING THE PHOSPHATIDE PRECIPITIN TEST IN TUBERCULOSIS[1,2]

With a Study of Two BCG-Vaccinated Children

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The importance of the epithelioid cell in tuberculosis is derived from the relationship it bears to the tubercle bacillus. Within the epithelioid and Langhans giant cells the acid-fast organisms seem to survive and even multiply with little if any difficulty. The derivation of the epithelioid cell from the monocyte of blood and connective tissues has been demonstrated (1) (2), and in both experimental and clinical tuberculosis the monocyte-lymphocyte ratio in the blood may be used as an indication of progressing or retrogressing lesions in the tissues.

The phosphatide fraction A-3 (Anderson (3)), derived from the chemical analysis of the tubercle bacillus, when introduced directly into the tissues of normal laboratory animals, produces epithelioid cells and Langhans giant cells analogous to those found in tuberculous lesions; the specificity of the reaction has been more characteristic and the tissue proliferation more extensive than that from any other partition thus far tested biologically (4). It has seemed possible, therefore, that the lipoids, and particularly this portion of the lipoid, may be principally responsible for the new formation of epithelioid tissue in the disease.

When, however, the phosphatide fraction is injected intravenously in small antigenic doses, the tissue response varies in different animals quite independently of the total dosage. For example, one rabbit (R682) received 175 mgm. of this fraction in divided doses of 25 mgm. each at four-day intervals. The monocyte-lymphocyte ratio before the phosphatide was given was 0.181; twelve days following the last intravenous

[1] From the Laboratories of The Rockefeller Institute for Medical Research, the Department of Pediatrics, Cornell University Medical College, and the New York Nursery and Child's Hospital.

[2] This study is a part of a coördinated investigation being conducted under the auspices of the National Tuberculosis Association.

injection the M/L index was 0.531. All of the organs upon postmortem examination showed small foci of epithelioid and Langhans giant cells. Another rabbit (R695) received at the same time a total of 150 mgm. of the phosphatide in 25-mgm. doses. The original M/L index was approximately the same as in the preceding animal, 0.179. After the series of intravenous injections the M/L ratio was 0.093, and on postmortem examination no new tissue proliferation was apparent in any of the organs. As small an amount of phosphatide as 5 mgm. has produced definite foci of new epithelioid cells in certain rabbits, while, as has been indicated, amounts ranging from 30 to 150 mgm. in other animals have been neutralized or eliminated without tissue reaction.

This difference in the manner of dealing with the tuberculo-phosphatide on the part of individual animals may be related to the well-known variations in resistance of normal stock rabbits or guinea pigs to identical dosages from known bovine and human strains of tubercle bacilli. Certain constitutions seem to be able to limit tubercle-formation and progressive disease under conditions apparently identical with those in which others show no such power of resistance. To be able to analyze and to know the factors governing the response of the individual to tuberculous infection would be the first step toward a more effective control of the disease.

It would seem that the animal body must either speedily eliminate the products of metabolism and catabolism of the tubercle bacillus, or effectively neutralize them, if a foreign-body, cellular, phagocytic response in the tissues, that is, tubercle-formation, is to be avoided. We have not studied the body excreta for evidence of the relative powers of elimination which different individuals may possess, but we have accumulated data with reference to the ability of certain of the body fluids to flocculate and precipitate the phosphatide *in vitro*, both from the experimental animals mentioned above, which had received the phosphatide in antigenic doses, and from animals and patients suffering from tuberculosis.

Though the rabbit has given us an inconstant antibody response to the phosphatide, with a varying titre (5) (6), this was to be anticipated from the fact that more than 60 per cent of the 40 rabbits given intravenous antigenic injections showed a cellular reaction in the tissues, and tuberculosis in this species is primarily a cellular disease, with little or inconstant development of the toxic and allergic phases. However, a definite increase in the precipitating power of the blood-serum for tuberculo-

phosphatide has frequently accompanied a maintained low M/L index in the peripheral blood in rabbits, which at autopsy showed no new tissue-formation. Moreover, either active or passive immunization with this fraction prolongs the average survival period in infected rabbits over that of the untreated tuberculous controls (7). Consequently, we have felt that the demonstration of the presence of antibodies to the phosphatide may signify an ability to neutralize, at least in part, this lipoid from the microörganism, which we now know to have the power, when in the tissues, of stimulating tubercle-formation. With the antibodies produced in rabbits, which have reacted serologically to intravenous phosphatide, it has been possible to demonstrate by the precipitin reaction the uncombined lipoid in body fluids from tuberculous animals and persons with progressive disease. Rabbits, in general, however, react so poorly and erratically to the phosphatide, when used as an antigen, that attempts are being made with other species to secure a serum with precipitating and complement-fixing antibodies of greater constancy and higher titre.

As an example of the type of study, which we feel may ultimately contribute something of value to our better understanding of the tuberculous process as it occurs in the human individual, we may cite a series of observations carried out this spring upon two children, each receiving an intracutaneous vaccination with *BCG* (*Bacillus Calmette-Guérin*). The opportunity for this study was afforded through the courtesy of Drs. W. H. Park and Camille Kereszturi of the New York Board of Health. The children were selected and vaccinated by Dr. Kereszturi in the course of the work with *BCG*, which is being conducted in New York City under Dr. Park's direction, and the children were kept throughout the period of observation on Dr. Schloss's service at the New York Nursery and Child's Hospital under Dr. Moore's supervision.

The chart of case 1 covers the laboratory observations during a two weeks' control period prior to the *BCG* vaccination, and the three months' period immediately following. The case history is appended at the end of this discussion. All of the blood studies were made with the supravital technique at the same time of day and with the same relation to meals. The results recorded on the charts are the total numbers of cells of each type. There was a fall of approximately 1,000,000 red blood cells and 15 per cent haemoglobin (Newcomer) during the first two months of the period following vaccination, with recovery during the third month. The greatest rise in monocytes came at the end of the sixth week and was associated with fever, but the fluctuations in the

lymphocytic series were much greater than any noted at any time in the monocytes. Most of the peaks in the curve representing the M/L index came as a result of low lymphocytes. A smoothing of the curves of the different types of white blood cells would reveal no general trends in any of the three groups. The points at which the M/L ratio reached 0.6, when considered in terms of the whole curve, probably represent but normal fluctuations for this age. The results of the precipitin tests performed on the blood-serum are recorded along the top of the chart. The plain columns represent the titre of the serum with phosphatide from the H37 human strain of tubercle bacillus; the cross-hatched columns indicate the titre with phosphatide of bovine origin. Three weeks following the *BCG* inoculation the precipitin titre of the blood-serum, which had been running between 1–40 and 1–80 (original suspension 1 per cent), suddenly rose to 1–1280. Figure 3, plate 1, is a photograph of the 24-hour reading taken at this time. On the same day 0.1 mgm. of Old Tuberculin gave a positive Mantoux reaction. The titre of the precipitin reaction remained the same the following week and the tuberculin skin test was positive to 0.02 mgm. The nodule, which formed at the site of injection, ruptured at the end of the first month. Direct smears of the discharge at this time showed from six to eight acid-fast organisms per oil-immersion field, and cultures on Petroff's gentian-violet-egg medium gave typical colonies. The guinea pig inoculated showed a skin reaction at the end of three months, and at autopsy the inguinal lymph nodes were enlarged and caseous, and revealed acid-fast organisms. Continued studies in culture and by animal passages are being made of the organism. The highest antibody titre was recorded at the end of the fifth week, at this time the reaction with bovine phosphatide being positive in a dilution of 1–2560, that with the H37 phosphatide 1–1280. The reaction has remained positive at a level considerably above the preinoculation point, though with some tendency to decrease.

The second case (see chart, case 2) has been followed with observations similar to those recorded above. The red blood cells and haemoglobin remained at approximately the same level throughout the period of observation. The M/L index rose somewhat during the third week, due to a fall in lymphocytes with possibly a slight rise in monocytes. The neutrophilic leucocytes were elevated, coincident with a transient upper-respiratory infection. But at the end of two months the white blood cell relationships were approximately the same as at the beginning. The precipitin tests in this case are of interest because of the promptness

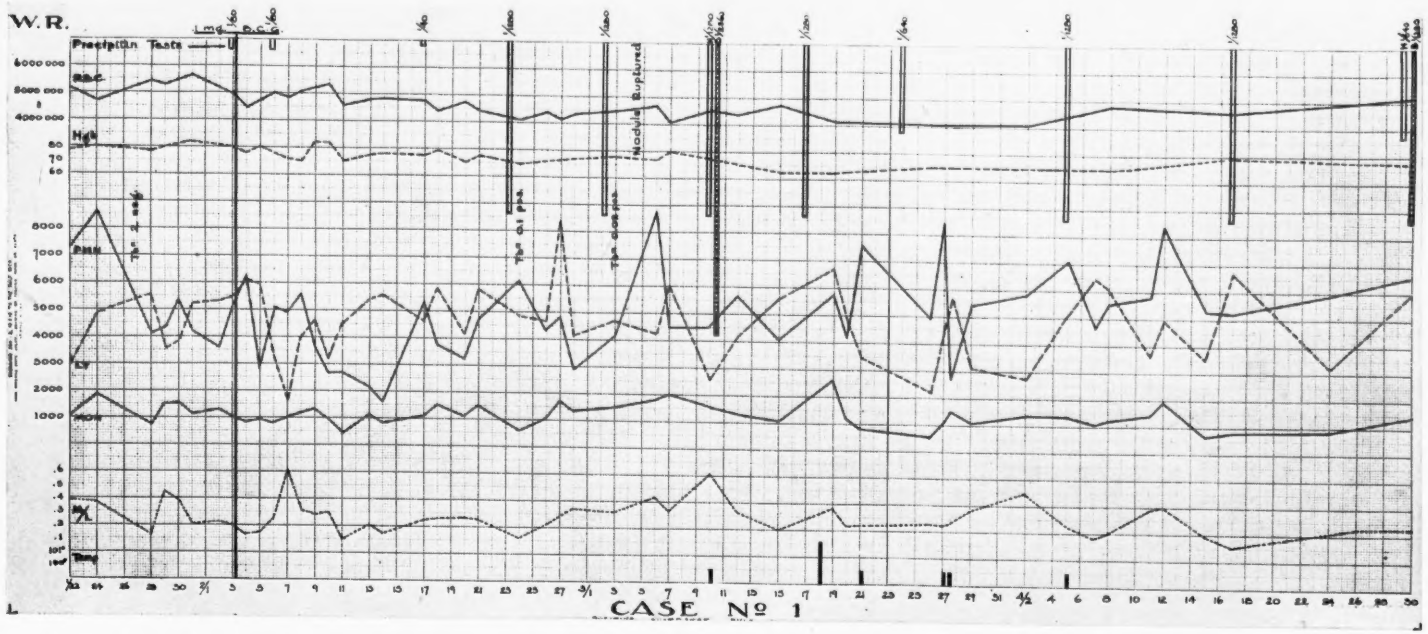

FIG. 1, Precipitin reaction, as read at 24 hours, with progressive dilutions of tuberculo-phosphatide layered over tuberculous pleural effusion. The final tube is the distilled-water control.

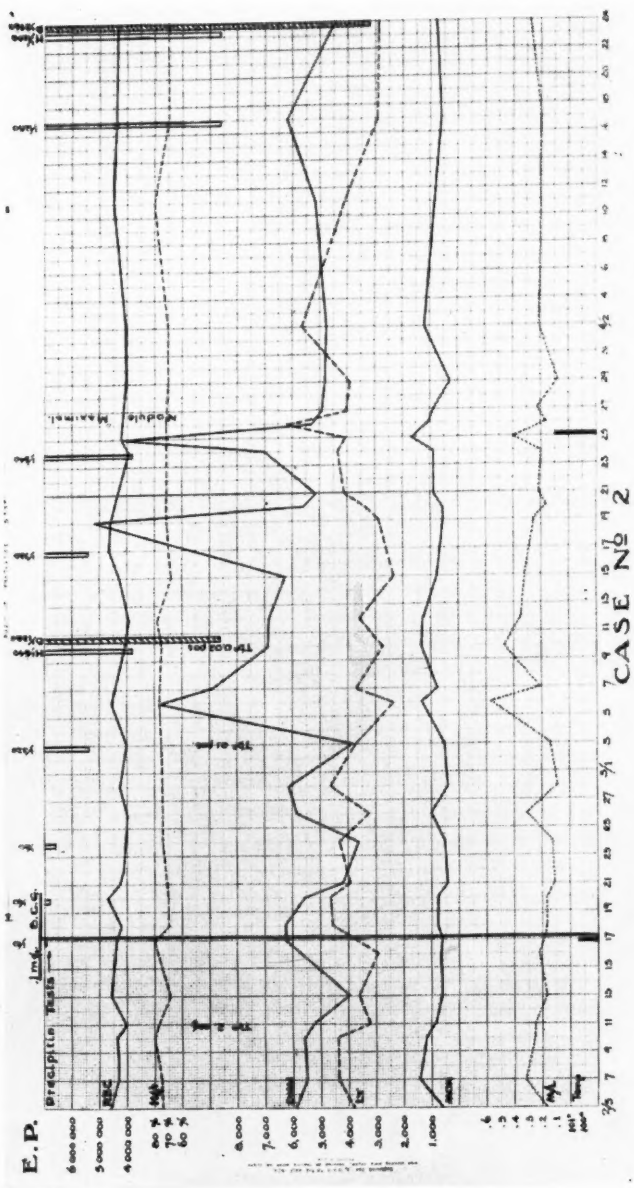

FIG. 2. The precipitin reaction, as read after 2 hours, with tuberculous spinal fluid. The reaction is frequently more pronounced than is shown in this instance, but the precipitin ring is always more delicate with spinal fluids than in the case of blood-serum and pleural effusion.

with which the titre began to increase from its preinoculation level of 1–10. On the third day it was 1–40, on the seventh 1–80, and on the fourteenth 1–320. The Mantoux test was found to be positive to 0.1 mgm. Old Tuberculin at the end of the second week. The titre has been higher for bovine tuberculo-phosphatide than for the phosphatide originating from the human strain when parallel tests were made. No free phosphatide antigen was demonstrable in either of these two cases at any time during the periods of observation. If interpretation of these findings is permissible in terms of the experimental studies recorded in the earlier part of this communication, we may say that with the evidence of increased ability to precipitate the phosphatide *in vitro* no change in the M/L index would be expected, because any rise in this ratio is but the reflection of a progressing tissue reaction, of epithelioid character, to bacillary products. What the result would be if and when the serological response is absent must await further studies of this type on *BCG* children. The number of blood counts on children vaccinated with *BCG*, as reported by Pittaluga and Garcia (8), are so few and incomplete that we feel no interpretation is justified. A large series of cases from among those inoculated by the New York Board of Health is being followed by Dr. Vera B. Dolgopol, with the fixed blood-smear technique.

In a control group of 10 children, negative to 2 mgm. Old Tuberculin, the precipitin titre of the blood serum has been: 2, 1–10; 1, 1–20; 4, 1–40; 2, 1–80; and 1, 1–320. In one instance in which the tuberculin test had been recorded as negative to 0.2 mgm. and the precipitin titre was 1–1280, a repetition of the Mantoux test was positive with 1 mgm. Further studies are being made in this case.

At the opposite extreme is a group of six children in which the tuberculosis was fatal, with confirmation of diagnosis by recovery of bacilli from inoculated guinea pigs and at autopsy. Table 1 presents the terminal blood findings. It will be seen that the two cases having the highest monocyte-lymphocyte ratio in the blood had the lowest antibody titre for phosphatide together with presence of uncombined antigen. The case with the antibody titre of 1–320 had one of the lowest M/L ratios. In the group of severe infections from a clinical standpoint are four cases, one of which showed an antibody titre of 1–1280, one 1–2560, and the other two 1–5000. The M/L index in these cases has been between 0.3 and 0.8, and these children are resisting their infection much more effectively than the six who succumbed promptly to the disease.

Two cases have been selected from several in which the M/L index and

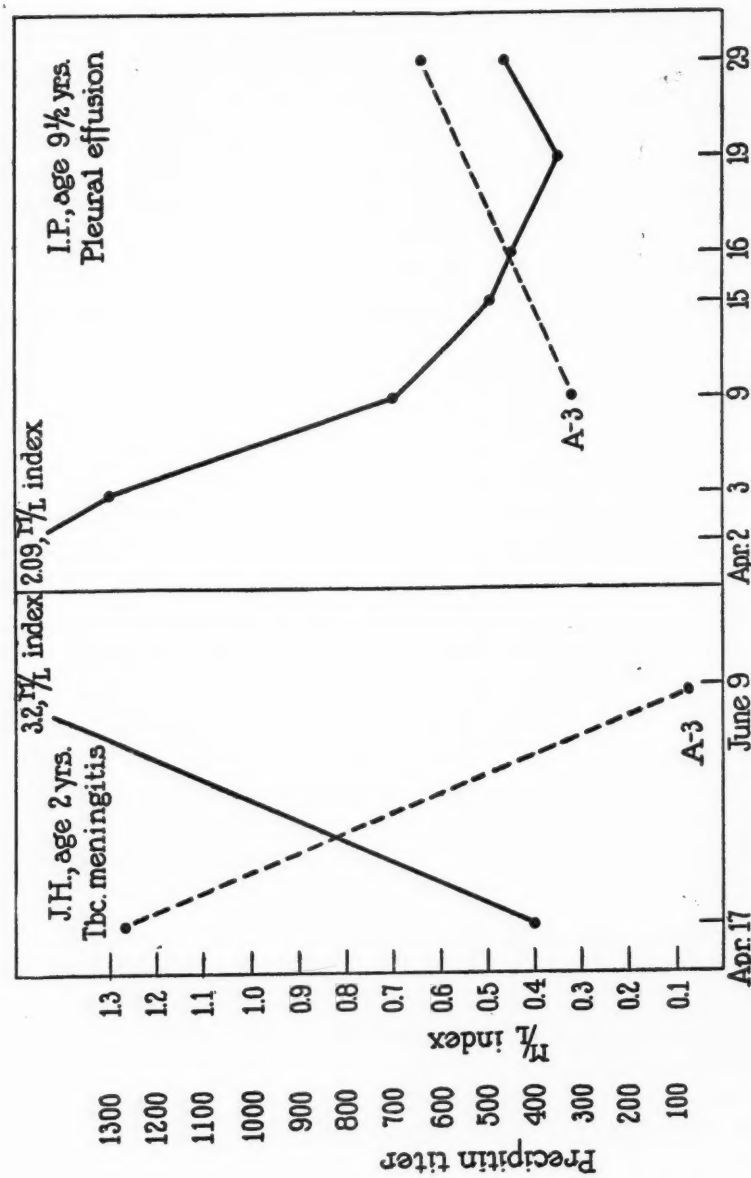

FIG. 3. The 24-hour reading made on the blood-serum of case 1 three weeks following intracutaneous inoculations with *BCG*.

blood precipitins have been correlated with the progress of the disease over a given period. Case 3, as seen on the chart, developed tuberculous meningitis. The M/L index in April of this year was 0.4 and the precipitin titre 1–1280; in June, with the development of meningitis, the antibody titre of the blood-serum fell to 1–40, with the spinal fluid showing 1–160, and the M/L ratio rose to 3.2. Case 4, aged 9½ years, was negative to 1 mgm. of Old Tuberculin in November, 1927. There was recent contact with the father, in the terminal stages of pulmonary tuberculosis. During the last week in March, 1930, there was sudden left thoracic pain with rapid development of pleural effusion. The M/L index shortly after admission April 2 was 2.09, temperature 101.5°, and the tuberculin reaction was ++++ to 0.2 mgm. With rest in bed the effusion resorbed completely in a short time, and the child's general

TABLE 1

Fatal cases of tuberculosis

CASE	M/L RATIO	PHOSPHATIDE ANTIBODY PRECIPITIN TITRE	UNCOMBINED ANTIGEN
		Blood or spinal fluid	
J. S.	4.5	1–40	+
J. H.	3.2	1–40	±
A. D.	2.7	1–160	±
L. O.	1.6	1–160	+
M. H.	0.75	1–160	−
C. L.	0.80	1–320	+

condition rapidly improved. The rapid fall in the M/L index is noted on the chart, together with a rise in the precipitin titre for phosphatide in the blood-serum. However, the suggestive initial rise again in the M/L index would point to a careful observation period for this patient in the immediate future.

These studies indicate the attempt that is being made to appraise, through two additional, though probably reciprocal, approaches, the reaction within the body to an established tuberculous infection; and perchance to aid in selected instances in the diagnosis of suspected cases in which the demonstration of the acid-fast organisms has been unsuccessful. Blood-sera, spinal fluids, pleural and joint effusions from many clinics and to the number of approximately 350 cases have been studied with the phosphatide precipitin tests during the past two years. Figure 1,

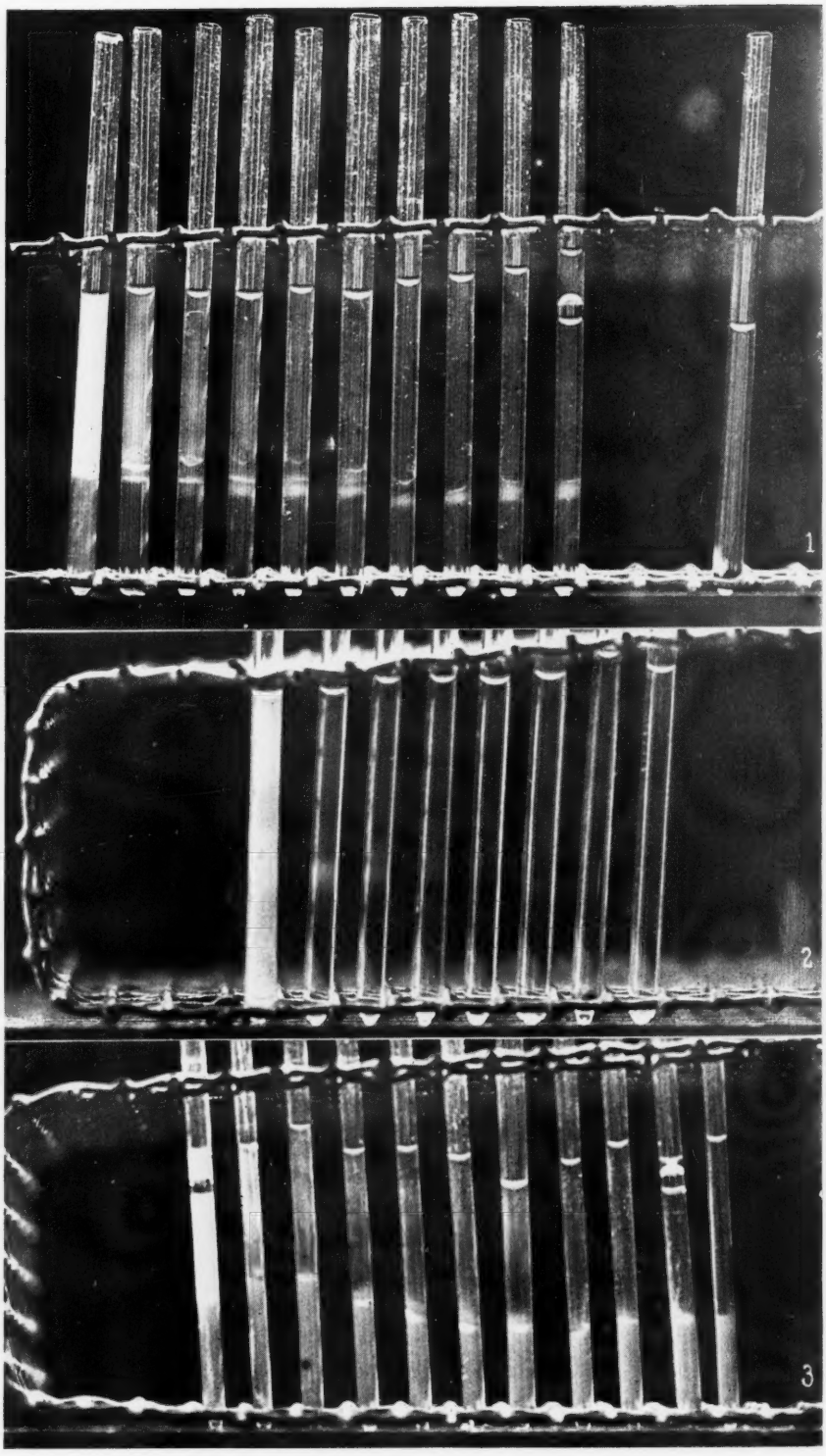

PLATE 1

plate 1, shows such an antibody test with a tuberculous pleural effusion; figure 2 represents the more delicate reaction of a tuberculous spinal fluid; and figure 3 is the reaction of the blood-serum with dilutions of phosphatide in case 1 three weeks after intracutaneous inoculation with *BCG*. While it has been impossible to establish and confirm the diagnosis, or to follow the outcome in many of the clinical cases, the results in known instances have been sufficiently suggestive in our hands to warrant further studies.

Case Reports

Case 1: W. R. *Family History:* The father has tuberculosis at the right apex. Sputum examinations have been positive repeatedly. He was in contact with the patient for only 2½ weeks when the child was 2 to 4½ weeks old. The father was then admitted to a hospital and has remained in institutions ever since. He has not visited the child at any time. The mother and a child of 2½ years are apparently well. A third child died a few minutes after birth. *Past History:* The patient was born August 1, 1929, at term, weighing 4.390 kg. For 6 weeks he was at home and breast-fed. From this time on he was boarded in several different boarding homes. He was supposedly fed a standard brand of condensed milk. He was probably not taken out of doors, nor given adequate codliver oil. He had no illnesses except an occasional respiratory infection. He was seen by Dr. Kereszturi, January 10, 1930. Intracutaneous tuberculin, 2 mgm., was negative at that time and again on January 27, at the New York Nursery and Child's Hospital. *Period of Observation:* The infant was admitted to the New York Nursery and Child's Hospital January 20, 1930. At this time physical examination showed marked pallor, the musculature was of poor tone, and the infant was inactive. He did not look acutely ill. His weight was 6.828 kg., length 68 cm., head circumference 42.5 cm., and thorax 40.5 cm. The head was markedly flattened posteriorly, with large parietal bosses, and showed slight craniotabes. The anterior fontanelle was 3.5 cm. wide; the posterior fontanelle was not open. The patient had no teeth. The tonsils were rather large and slightly red. Cervical lymph nodes, 0.5 cm. in diameter, ran in chains along the posterior border of the sternocleidomastoid muscles. The chest showed enlargement of the costochondral junctions and slight flare of the ribs. Over the lungs the percussion note and breath-sounds were normal. There were no râles. The heart was normal. The abdomen was flaccid, the spleen just palpable, and the liver border 2 cm. below the costal margin. Inguinal lymph nodes were not palpable on either side. *February 3, 1930:* 0.1 mgm. *BCG* vaccine was injected by Dr. Kereszturi. The injection was made on the lateral surface of the left thigh. Most of the suspension was introduced intracutaneously. Because of the child's struggling, however, a small

amount entered the subcutaneous tissue. There was redness, 1 cm. in diameter, about the point of injection for 48 hours, which then faded. After 7 days a nodule formed, which progressively increased in size. At 3½ weeks there was an area of deep induration, about 1.5 cm. in diameter. Only after this time did the skin become reddened; finally a small central pustule formed. Thirty days after the injection this ruptured, exuding thin pus. Six to eight acid-fast organisms per field were seen in this material, and they grew typically on Petroff's gentian-violet-egg medium, after treatment with sulphuric acid. From this time the lesion repeatedly scabbed over and broke down again. Four months after the injection there was still an area of induration of 1.5 cm. This was purplish in color, with a small crater in the centre. A guinea pig, inoculated on March 3, 1930, with material from this lesion, developed a positive tuberculin reaction, and at autopsy, 90 days following injection, acid-fast organisms were recovered from enlarged, caseous, inguinal lymph nodes. Nineteen days after injection the left inguinal nodes in the patient were first noted as palpable and progressively increased in size, until at the present time, after four months, they are 0.5 cm. in diameter. No lymph nodes have been felt on the right side at any time. Tuberculin intracutaneously, 0.1 mgm., on the 21st day was positive; 0.02 mgm. on the 28th day was also positive. The child's general course during his hospital stay was marked by constant respiratory infections. Nasal discharge existed at times, the throat was almost always reddened. He had a loose cough, and frequently coarse moist râles were heard. In association with these respiratory infections, his temperature rose to 100° for a day on several occasions, as noted on the chart. At one time he developed numerous pustules in the diaper area. In treatment of this he was exposed to a carbon lamp and developed a temperature of 102.6°, not apparently due to any other cause. It was noted that at this time there was a transitory increase of monocytes. He developed chickenpox on April 13 and was sent to Willard Parker Hospital, but was not seriously ill at any time. He received the usual diet for a child of his age, with 8 cc. of codliver oil. He was not given ultraviolet light or ergosterol. Food was poorly taken at first. He gained only 1.2 kg. in his four-month hospital stay, but his general condition greatly improved, due to the healing of his rickets. X-rays were taken at weekly intervals and the readings of Dr. Harriet C. McIntosh, of the X-ray Department, Nursery and Child's Hospital, have been negative up to the present.

This case will be followed indefinitely.

Case 2: E. P. *Family History:* The father has tuberculosis. His symptoms began 6 months before the birth of this child. He had two haemoptyses, coughed, and lost weight. He had been in Otisville Sanatorium since before the birth of this child. He coughs little now and is gaining weight. He

visits his home for five or six days every three months; during these times he does not come in intimate contact with the child. The mother has been examined repeatedly and is well. Of three older living children, two have a positive and one has a negative Pirquet test. *Past History:* The patient was born September 7, 1927. The delivery was normal and his infancy uneventful. He had chickenpox and pertussis at 1½ years old. Tuberculin, 2 mgm., was negative on January 15 and again on February 11, 1930. *Period of Observation:* Physical examination on admission, February 4, 1930, showed a healthy-looking, active child. He had a temperature of 100°, nasal discharge was present, and the tonsils were rather large and slightly red. There were lymph nodes, 0.5 cm. in diameter, along the posterior borders of the sternocleidomastoid muscles. The lungs were negative. Inguinal lymph nodes were pea-sized on both sides. *February 17, 1930:* 0.1 mgm. *BCG* vaccine was given intracutaneously by Dr. Kereszturi. A superficial nodule formed at the site of injection, which at 15 days showed a red areola but no deep induration: 1.5 cm. deep induration developed on the 35th day and the centre of the lesion was crusted over, looking as if a little pus was beneath. The scab, when it dropped off, left a shallow excavation which has repeatedly crusted over. No bacilli were seen on smear. The left inguinal lymph nodes became larger than those on the right from the 17th day on. The largest reached 1.1 cm. in diameter and was the most lateral of the left inguinal group. The tuberculin test, 0.1 mgm., was positive on the 14th day; 0.02 mgm. was very slightly positive on the 21st day. The respiratory infection present on admission quickly subsided, but the child had a number of recurrences during his hospital stay, marked by very profuse nasal discharge. The temperature reached 100° on six occasions and once 102°; otherwise he was afebrile. He became pale and did not eat well. Three ultraviolet-light treatments were given. After discharge, March 28, 1930, when he was out-of-doors constantly, his general condition improved greatly. Weekly X-ray examinations were reported negative by Dr. McIntosh.

This case will be followed indefinitely.

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SERUM-CALCIUM IN PULMONARY TUBERCULOSIS[1,2]

JACOB KAMINSKY AND DORIS L. DAVIDSON

The view of the older writers, that tuberculosis is accompanied by a dimineralization, has stimulated considerable study on calcium metabolism in this disease. Recent reports did not substantiate, in the main, the above view. Many investigators, however, in studying the blood-calcium in tuberculosis, have noted lowered calcium values with advancing disease.

Halverson, Mohler and Bergheim (1) found slightly lowered values in progressing cases. Greisheimer and Van Winkle (2) noted lower calcium values in moderately advanced and far-advanced C cases. Brockbank (3) found high serum-calcium values in arrested cases and very low calcium values in acute cases. Teplitz (4) found a marked loss of calcium in the toxic type of cases. Dolgopol (5) found an average serum-calcium content below the average normal range in the far-advanced C group. In a small series (10 cases) of moderately advanced and far-advanced pulmonary tuberculosis previously studied by us (6), an average serum-calcium below normal was noted.

The present report is based on serum-calcium determinations in an unselected group of 154 patients with pulmonary tuberculosis under treatment at the Rutland State Sanatorium. It included 89 men and 65 women. Their ages ranged between 17 and 64 years. All stages of the disease were represented and some of the patients also had extrapulmonary complications.

The serum-calcium was determined by the method of Kramer and Tisdall (7). Blood specimens were taken from a vein three to four hours after breakfast.

RESULTS

The serum-calcium concentration in the entire series ranged from 7.52 mgm. to 11.62 mgm. per 100 cc. of blood-serum and the average was

[1] From the laboratory of the Rutland State Sanatorium, Rutland, Massachusetts.
[2] Read before the Trudeau Society of Boston, December 9, 1930.

9.99 mgm. The normal range of serum-calcium is generally given as 9 to 11 mgm. per 100 cc. of blood-serum (8). Of our cases 10.38 per cent had a serum-calcium below 9 mgm.: that is, below the lowest figure in the normal range. In 46.1 per cent of our cases the serum-calcium was below 10 mgm. and in 53.9 per cent of our cases the serum-calcium readings were 10 mgm. or above.

TABLE 1

Serum-calcium concentration in pulmonary tuberculosis, all stages

NUMBER OF CASES	RANGE	AVERAGE	BELOW 9 MGM.	BELOW 10 MGM.	10 MGM. OR ABOVE
	mgm.	*mgm.*	*per cent*	*per cent*	*per cent*
154	7.52–11.62	9.99	10.38	46.1	53.9

Our series showed a greater frequency of lower calcium values when compared with figures given for normal individuals. This is brought out in table 2, where the results of serum-calcium determinations on normal subjects by Rosen and Krasnow (9), Matz (10) and Roe and Kahn (8), were analyzed and tabulated for comparison with the results in our series.

TABLE 2

Serum-calcium concentration in normal and tuberculous subjects

	NUMBER OF CASES	RANGE	AVERAGE	BELOW 9 MGM.	BELOW 10 MGM.	10 MGM. OR ABOVE
		mgm.	*mgm.*	*per cent*	*per cent*	*per cent*
Series of Rosen and Krasnow	50* (normal subjects)	10.7 to 13.2	11.66	0	0	100
Series of Matz	50 (normal subjects)	9.0 to 12.0	10.28	0	28	72
Series of Roe and Kahn	50 (normal subjects)	9.0 to 11.6	10.15	0	46	54
Series of Kaminsky and Davidson	154 (tuberculous subjects)	7.52 to 11.62	9.99	10.38	46.1	53.9

* The figures for this series were computed on the basis of 49 cases.

It will be noticed that in none of the normal series were there serum-calcium readings below the normal range. The relative frequency of higher and lower calcium values in the tuberculous series corresponds fairly closely with that of the series of Roe and Kahn. However, the percentage of lower calcium values was considerably higher in our series (46 per cent below 10 mgm.) than in the series of Matz (28 per cent below 10 mgm.) and in that of Rosen and Krasnow (no reading below 10 mgm.).

Our results were studied further with a view to determine whether there is any relationship between serum-calcium concentration and the extent and activity of disease, the bacillary content of the sputum, a tendency to haemoptysis and age and sex of the patient. The results are presented in tables 3 to 8.

TABLE 3

Serum-calcium concentration in the different stages of pulmonary tuberculosis

STAGE	NUMBER OF CASES	RANGE	AVERAGE	BELOW 9 MGM.	BELOW 10 MGM.	10 MGM. OR ABOVE
		mgm.	*mgm.*	*per cent*	*per cent*	*per cent*
I	12	9.28–11.4	10.24	0	33.33	66.67
II	72	7.88–11.62	10.1	4.16	40.27	59.73
III	70	7.52–11.4	9.96	18.57	54.28	45.72

A lowering of the serum-calcium level was noted with the increase of the extent of the disease. The minimal cases showed the highest average of serum-calcium, the smallest percentage of readings below 10 mgm. and the highest percentage of serum-calcium readings of 10 mgm. and above. There was some decline in the figures for moderately advanced cases and a considerable fall in the serum-calcium values in the far-advanced cases.

The influence of activity of the disease on the serum-calcium concentration was quite apparent. Cases in the active group showed a lower average and a greater percentage of lower calcium values than those of the quiescent group.

TABLE 4

Serum-calcium concentration in active and quiescent cases

	NUMBER OF CASES	RANGE	AVERAGE	BELOW 9 MGM.	BELOW 10 MGM.	10 MGM. OR ABOVE
		mgm.	*mgm.*	*per cent*	*per cent*	*per cent*
Active cases	106	7.52–11.4	9.86	12.26	51.88	48.12
Quiescent cases	48	8.12–11.62	10.24	6.25	31.25	68.75

The group of patients with positive sputum showed a lower average and a greater frequency of lower serum-calcium values than the group with negative sputum.

TABLE 5

Serum-calcium concentration in cases of pulmonary tuberculosis with positive and with negative sputum

	NUMBER OF CASES	RANGE	AVERAGE	BELOW 9 MGM.	BELOW 10 MGM.	10 MGM. OR ABOVE
		mgm.	*mgm.*	*per cent*	*per cent*	*per cent*
Cases with positive sputum.....	102	7.88–11.3	9.87	13.73	50.98	49.02
Cases with negative sputum.....	52	7.52–11.62	10.2	3.84	36.53	63.47

Cases with a history of haemoptysis and those without a history of haemoptysis showed about the same relative frequency of higher and lower serum-calcium values.

TABLE 6

Serum-calcium concentration in cases with a history of haemoptysis and in those without a history of haemoptysis

	NUMBER OF CASES	RANGE	AVERAGE	BELOW 9 MGM.	BELOW 10 MGM.	10 MGM. OR ABOVE
		mgm.	*mgm.*	*per cent*	*per cent*	*per cent*
Cases with a history of haemoptysis.	70	7.52–11.62	10.01	8.57	45.71	54.29
Cases without a history of haemoptysis.....	84	8.12–11.4	9.98	10.18	45.23	54.77

There was little difference in the serum-calcium values in the sexes. The male group showed a greater percentage of cases with serum-calcium readings below the average normal range. However, 12 out of the 14 cases that showed these low calcium values belonged to the active group.

TABLE 7

Serum-calcium concentration in the sexes

	NUMBER OF CASES	RANGE	AVERAGE	BELOW 9 MGM.	BELOW 10 MGM	10 MGM. OR ABOVE
		mgm.	*mgm.*	*per cent*	*per cent*	*per cent*
Men.....	89	7.52–11.4	9.94	15.84	46.06	53.94
Women.....	65	8.33–11.62	10.05	3.07	46.15	53.85

The age-groups 17 to 26 and 27 to 36 showed little difference in serum-calcium readings from those obtained for the entire series. The age-group 37 to 46 showed the highest serum-calcium concentrations and the age-group 47 to 64 showed the lowest serum-calcium concentrations.

TABLE 8

Serum-calcium concentrations in the different age-groups

AGE-GROUP	NUMBER OF CASES	RANGE	AVERAGE	BELOW 9 MGM.	BELOW 10 MGM.	10 MGM. OR ABOVE
		mgm.	*mgm.*	*per cent*	*per cent*	*per cent*
17–26	71	7.52–11.4	9.97	11.26	46.47	53.53
27–36	43	8.42–10.78	9.97	4.65	48.83	51.17
37–46	21	8.20–11.3	10.21	4.76	28.57	71.43
47–64	19	8.23–11.62	9.80	26.31	57.89	42.11

The serum-calcium was also determined in a group of 16 patients who were receiving codliver oil and tomato juice for periods ranging from three weeks to about 12 months. The dosage of codliver oil varied from three drams to one and one-half ounces daily. The results of the serum-calcium determinations in this group are presented in table 9.

TABLE 9

Serum-calcium concentration in cases of pulmonary tuberculosis receiving codliver oil

PATIENT	AGE	STAGE	DAILY DOSE OF CODLIVER OIL	PERIOD OF TREATMENT	SERUM-CALCIUM IN MILLIGRAMS
V. S.	20	III	3 drams	Apr. 10, 1930–Aug. 28, 1930	11.17
G. C.	19	III	6 drams	May 9, 1930–Aug. 28, 1930	9.34
W. P.	36	III	6 drams	June 20, 1930–Aug. 28, 1930	11.85
A. D.	22	II	6 drams	July 16, 1930–Aug. 28, 1930	12.76
J. M.	26	III	6 drams	June 6, 1930–Aug. 28, 1930	12.08
T. McN.	40	III	6 drams	June 16, 1930–Aug. 25, 1930	12.76
C. L.	30	III	6 drams	Jan. 14, 1930–Aug. 25, 1930	11.83
V. A.	21	II	1½ ounces	June 16, 1930–Aug. 28, 1930	10.48
J. W.	31	II	1½ ounces	June 16, 1930–Aug. 28, 1930	9.8
F. W.	29	III	1½ ounces	May 5, 1930–Aug. 25, 1930	11.62
N. P.	21	II	1½ ounces	June 16, 1930–Aug. 25, 1930	11.83
H. S.	29	II	1½ ounces	June 6, 1930–Aug. 25, 1930	13.45
M. G.	30	III	1½ ounces	Aug. 28, 1929–Aug. 25, 1930	12.29
P. P.	23	III	1½ ounces	Dec. 24, 1929–Aug. 25, 1930	11.6
D. G.	19	III	1½ ounces	Aug. 3, 1930–Aug. 25, 1930	10.9
M. M.	20	III	1½ ounces	Aug. 3, 1930–Aug. 25, 1930	12.29
Average					11.62

The average calcium concentration for the group of patients receiving codliver oil was 11.62 mgm. per 100 cc. of blood serum, thus exceeding the average for the untreated tuberculous group by 1.63 mgm. There were no readings below the normal range and only 2 cases showed a serum-calcium below 10 mgm. In 12 cases the serum-calcium was above 11 mgm. and in 6 out of these 12 cases the serum-calcium was above 12 mgm.

DISCUSSION

The average serum-calcium concentration in a group of 154 tuberculous subjects was lower than normal and the incidence of low calcium values was higher in the tuberculous group than in normal subjects. However, further study of our results showed that the lower values obtained for the entire group were due, in a large measure, to the more active cases in the series. Thus we found that minimal cases and quiescent cases showed little variation in the serum-calcium concentrations from those of normal subjects. On the other hand, there was a considerable fall in the serum-calcium level in the far-advanced cases; active cases showed lower calcium values than quiescent cases and in cases with positive sputum there was a higher incidence of lower calcium values than in cases with negative sputum.

There seemed to be no relationship between a history of haemoptysis and the serum-calcium concentration. The relative frequency of higher and lower calcium values was about the same in both groups. Neither was there much difference in the serum-calcium concentration between the sexes. The preponderance of cases with serum-calcium readings below the normal range in the male group might be explained by the greater number of active cases in this group.

The age-group 37 to 46 had the highest serum-calcium readings and the age-group above 47 had the lowest readings. Since the number of active cases was about the same in both groups, the influence of age might be considered in this instance.

Seventy-five per cent of the cases receiving codliver oil showed a serum-calcium concentration above the uppermost level of the normal range (above 11 mgm.) and in 6 cases the serum-calcium ranged from 12.08 to 13.45 mgm.

Attention is invited to the mild hypercalcaemia in some of the above cases. Furthermore, since a single serum-calcium determination portrays only the calcaemia at that particular instance, the possibility of

even higher grades of hypercalcaemia in patients receiving codliver oil for long periods cannot be excluded.

SUMMARY

1. Minimal cases of pulmonary tuberculosis and cases with quiescent lesions showed little variation in their serum-calcium values from those of normal individuals.

2. Active cases of pulmonary tuberculosis and cases with extensive lesions showed a higher incidence of low serum-calcium values and a lower average serum-calcium concentration than normal subjects.

3. Cases with a history of haemoptysis and those without a history of haemoptysis showed about the same relative frequency of higher and lower serum-calcium values.

4. There was little difference in the serum-calcium values between the sexes.

5. The age-group 37 to 46 showed the highest and the age-group 47 to 64 the lowest serum-calcium values.

6. Tuberculous patients receiving codliver oil showed a high incidence of serum-calcium values above the uppermost level in the normal range. The average serum-calcium concentration in the group of patients receiving codliver oil was higher than in the untreated group.

7. In 6 patients receiving codliver oil for periods ranging from 3 weeks to about 12 months, a mild degree of hypercalcaemia was noted.

We wish to express our appreciation to the Medical Staff of the Rutland State Sanatorium for the coöperation which was very helpful to us in carrying out this investigation.

We wish to thank Miss Marcelle Duçot, laboratory technician, for her assistance during this investigation. We appreciate the spirit and conscientious way in which such assistance was rendered.

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THE PROPORTIONS OF WATER AND OTHER INORGANIC CONSTITUENTS IN THE HEART MUSCLE OF TUBERCULOUS INDIVIDUALS[1]

L. C. SCOTT

Determinations of the inorganic constituents of heart muscle are very few in number. This is especially true with reference to specific disease groups. None for the latter have, so far as I have been able to ascertain, been carried out, though many analyses for fat, protein, water, total nitrogen, etc., are reported. The most extensive tabulation of this sort was published by Domagh (1) in 1924 and another by Emmerich and Domagh (2) which is virtually a repetition of the former work.

Since then isolated analyses, more or less complete, have been made: that of Harrison, Pilcher and Ewing (3) dealing with the relation of potassium salts in cardiac muscle to oedema, and the work of Norn (4), done in connection with potassium in the heart and with potassium excretion. Finally, one analysis, evidently on a single human heart and quite complete for inorganic constituents, included in a series of similar determinations on a variety of tissues from the lower animals, has been published by Le Matte and coworkers (5).

Domagh is the only one who specifically mentions the disease process to which the person succumbed, and of his 37 analyses for water, total nitrogen, protein, solids, etc., the only ones of interest here are those of the water content of tuberculous hearts.

In classifying Domagh's table into groups it has been found that the mean water content of 6 hearts from tuberculous persons was 81.34 per cent; arteriosclerotic cases, of which there were six, averaged 80.10 per cent; endocarditis 80.00 per cent with four, and pneumonia 78.69 per cent also with four determinations. Other groups are not characteristic, but one group of 10 miscellaneous diseases totals an average of 80.29 per cent. These are only cited to indicate that, while the number is small, there appears to be something distinctive about tuberculosis in so far as cardiac

[1] From the Heart Station of the New Orleans Charity Hospital and the Department of Tropical Medicine, Tulane University Medical School, New Orleans, Louisiana.

TABLE 1

Tuberculosis cases

NUMBER	SEX	AGE	COLOR	MOISTURE	ASH	P_2O_5	Fe_2O_3	CaO	MgO	K_2O	Na_2O	TYPE
				per cent	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	
58	F.	23	B.	81.71	4.008	1.629	0.116	0.096	0.118			Pulmonary
59	F.	52	B.	79.01	3.652	1.661	0.083	0.071	0.127			Pulmonary
60	F.	44	B.	83.19	4.664	1.882	0.062	0.111	0.148			Miliary
61	M.	50	B.	79.72	4.695	1.940	0.143	0.030	0.074			Pulmonary
69	M.	44	W.	82.24	4.422	1.880	0.148	0.092	0.155			Pulmonary
71	F.	25	B.	79.98	4.224	1.760	0.120	0.088	0.146			Pulmonary
75	F.	21	B.	81.80	3.682	1.679	0.100	0.044	0.127			Pulmonary and intestinal
77	M.	39	B.	79.46	4.834	2.025	0.153	0.067	0.154			Pulmonary
92	M.	23	B.	84.04	4.672	2.123	0.044	0.056	0.171			Miliary and pulmonary
93	M.	44	B.	79.17	4.137	1.826	0.047	0.057	0.130			Pulmonary
97	M.	47	B.	78.92	4.621	2.128	0.080	0.043	0.154	0.946	1.151	Pulmonary
101	F.	17	B.	80.29	4.816	2.075	0.053	0.020	0.186	1.392	1.122	Miliary
105	M.	51	W.	82.12	5.055	1.830	0.083	0.068	0.151	1.026	1.588	Pulmonary
113	M.	19	B.	84.91	5.592	2.074	0.052	0.092	0.137	0.875	1.760	Pulmonary
Mean				81.18	4.505	1.894	0.092	0.067	0.141	0.985	1.430	
Probable error of mean				±0.341	±0.093	±0.025	±0.007	±0.005	±0.005			
Mean deviation				1.512	0.411	0.130	0.030	0.021	0.020			
Standard deviation				1.890	0.514	0.163	0.037	0.026	0.025			

TABLE 2

General diseases

NUMBER	SEX	AGE	COLOR	MOISTURE	ASH	P_2O_5	Fe_2O_3	CaO	MgO	K_2O	Na_2O	DISEASE
				per cent	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	
98	M.	70	W.	78.17	4.338	1.852	0.033	0.087	0.135	1.074	1.264	Arteriosclerotic senile gangrene
99	F.	39	B.	79.55	4.178	1.830	0.030	0.040	0.127	1.074	1.175	Carcinoma of cervix
102	M.	22	B.	79.65	5.350	2.468	0.083	0.030	0.187	1.402	1.227	Congestive heart failure
103	M.	66	B.	78.06	4.035	1.894	0.093	0.063	0.122	0.808	1.190	Diabetes mellitus
104	M.	47	B.	80.32	4.269	1.856	0.070	0.060	0.116	0.852	1.176	Cerebral haemorrhage
107	M.	60	W.	79.80	3.953	1.699	0.077	0.043	0.116	0.749	1.139	Syphilis, bronchopneumonia
108	M.	40	B.	78.38	4.279	2.011	0.133	0.027	0.115	0.698	1.212	Congestive heart failure
109	M.	80	B.	78.84	4.370	1.854	0.107	0.110	0.140	1.049	1.089	Bronchopneumonia
110	M.	60	B.	80.76	5.235	2.168	0.090	0.057	0.146	1.068	1.163	Syphilis, bronchopneumonia
111	M.	62	B.	80.57	4.828	2.077	0.070	0.070	0.156	0.941	1.114	Syphilis, congestive heart failure
112	M.	13	B.	77.25	4.710	2.387	0.097	0.053	0.164	1.129	1.233	Syphilis of central nervous system
114	M.	41	B.	81.12	4.883	2.071	0.060	0.053	0.151	1.138	1.307	Congestive heart failure
115	M.	42	B.	79.90	4.431	1.608	0.077	0.033	0.125	1.236	1.025	Syphilitic heart disease
116	M.	56	B.	79.17	5.003	2.028	0.053	0.040	0.169	1.427	1.009	Congestive heart failure
Mean				79.39	4.562	1.986	0.077	0.055	0.141	1.046	1.167	
Probable error of mean				±0.192	±0.074	±0.042	±0.005	±0.004	±0.004	±0.038	±0.015	
Mean deviation				0.850	0.334	0.186	0.021	0.018	0.018	0.170	0.066	
Standard deviation				1.063	0.418	0.232	0.027	0.022	0.022	0.212	0.082	

moisture is concerned. It will be shown that this factor receives a certain amount of corroboration from the results presented in the tables.

The determinations contained in tables 1 and 2 are taken from a large series of 69 analyses made on human heart muscle for moisture and ash, and, of these, 58 were not only examined for water and ash but also for P_2O_5, Fe_2O_3, CaO and MgO, and 33 for K_2O, and Na_2O.

Fourteen analyses on hearts from tuberculous persons were selected for comparison with a similar number dying of miscellaneous, predominantly cardiovascular, diseases. Unfortunately I am able to include only four determinations of K_2O and Na_2O in the table for tuberculous hearts. Only summaries of certain phases of the entire work have so far been offered for publication.

METHOD

The methods for determining the inorganic constituents of heart muscle have been fully described in an article which, it is hoped, will appear shortly. It is only necessary to mention very briefly the simple principles involved here.

Moisture was determined by drying 31–35 gm. of finely ground muscle tissue from the left ventricle, obtained as soon as possible after autopsy, to a relatively constant weight.

Ash was found by incinerating 5–10 gm. of dried muscle in a silica dish at as low a temperature as possible compatible with destruction of organic matter. The ash should be white or almost white and not have been melted.

P_2O_5 was precipitated in the nitric-acid solution of the ash with 25 per cent ammonium-molybdate solution according to the method of Woy given in Treadwell's textbook (6).

Iron could be quantitatively removed from the filtrate from the molybdenum precipitate with ammonia. Calcium is thrown down in the filtrate from the iron with ammonium oxalate, and finally magnesium is precipitated as the ammonium phosphate compound after the lime has been removed. The final weighings were made as the oxides of iron and lime and as the pyrophosphate of magnesium.

K_2O and Na_2O were determined separately by incinerating 5–10 gm. of dried tissue, solution of the ash with HCl, and the removal at one procedure of phosphates together with the alkaline-earth metals. The filtrate containing only the alkalies as chlorides was then diluted to 250 cc. in a measuring flask.

An aliquot portion of the dilution, 25 cc., representing either 0.5 or 1.0 gm. of the original dried muscle was evaporated to dryness with sulphuric acid and, after appropriate treatment of the mixed sulphates of Na and K with ammonium carbonate, they were weighed as such.

The amount of potassium in the mixture of sodium and potassium sulphates was found by the method of Neubauer (7), which control determinations with known quantities of C.P. sodium and potassium chlorides had shown to be very accurate and reliable.

The results of 28 of these analyses are embodied in tables 1 and 2. The percentages of ash, phosphates, iron, lime, magnesium, and the alkali oxides are expressed in terms of dry tissue.

DISCUSSION

It is recognized that the statistical constants for either of these series will at best be only approximate, but they have been added for the purpose of indicating the variability even within the relatively narrow limits. While there is both close agreement and discrepancy among the means of both tables 1 and 2, it is at once clear that the distinctive difference lies in the water content of the hearts from the tuberculous patients. Even when we compare them with arithmetical means from a large group which also includes these 14 tuberculous hearts, we still observe the characteristic difference. For instance the means for 58 hearts are H_2O, 80.13 per cent; ash, 4.509 per cent; P_2O_5, 1.855 per cent; Fe_2O_3, 0.085 per cent; CaO, 0.071 per cent; MgO, 0.137 per cent; while the K_2O and the Na_2O for 33 hearts were respectively 1.101 and 1.191 per cent. In both series the water content of the tuberculous hearts is much higher than in those from persons dying of the usual run of acute infectious and degenerative diseases.

The relatively high water content (81.34 per cent) of tuberculous hearts observed by Domagh leads him to conclude, on the rather slender evidence of only 6 determinations, that this was a typical condition for atrophic hearts. The 14 classified in table 1 seem, at any rate, to contribute some additional evidence in support of this assumption, and the mean water content does not greatly differ from the average of Domagh.

It is rather striking that the other inorganic constituents of tuberculous hearts show no marked deviation from the usual run. Perhaps the reason is that there are not the requisite number of analyses or that the analytical methods themselves are not sufficiently sensitive to detect the small differences. One would expect to find less of the alkali elements,

and for the four analyses the means are actually lower than those of table 2. But again the number is not sufficiently great for a proper comparison.

If one might hazard a theory as to the cause of this increased heart water content in tuberculosis it would seem fairly reasonable to assume that the reason lies in long-continued obstruction to pulmonary circulation.

CONCLUSIONS

The principal inorganic constituents of 14 hearts from tuberculous individuals agree fairly well with those of an equal number of hearts from persons dying of miscellaneous diseases with the sole exception of the water content. The latter is sufficiently in excess of the average found in other diseases to warrant the assumption that it is characteristic of this disease process, especially when it has been of comparatively long standing.

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CEREBRAL AIR EMBOLISM COMPLICATING ARTIFICIAL PNEUMOTHORAX

Report of a Case[1]

C. H. ANDREWS

Search of the available literature for information concerning cerebral air embolism reveals a dearth of material, especially from the English-speaking world.

Lillingston (1) discusses the matter very thoroughly, and quotes Wever's experimental work on monkeys in which the reactions obtained were very similar to those observed clinically. Reyer and Kohl (2) also discuss the condition in some detail and report 10 cases with two autopsies, and Bishop (3) reports one with autopsy. In two of these cases (Reyer and Kohl's fifth case, and Bishop's) air was actually introduced into the chest and the existence of cerebral air embolism was proved by autopsy. The clinical picture in these two cases was identical and in the absence of further data it appears reasonable to accept these two as most typical of embolism when it occurs as a complication of artificial pneumothorax.

These two cases occurred in patients who had many previous pneumothorax refills (left side) and in whom extensive adhesions were present. In each, 100 cc. of air was introduced under pressure, and pain occurred immediately at the site of puncture. The patient sat up, and then collapsed, unconscious. Tonic spasm of the right side of the face occurred, then of the extensors of the back and legs, and then of the diaphragm and abdominal muscles. Cyanosis and rapid pulse were present, and conjugate deviation of the eyes was noticed. Clonic convulsions of the muscles previously involved in the tonic spasm developed, followed by coma, and the convulsions became more frequent and death ensued. At autopsy oedema of the brain substance was found and the right subdural vessels were full of air-bubbles.

Reyer and Kohl's other cases and the one reported here present suffi-

[1] From the Fort Qu'Appelle Sanatorium of the Saskatchewan Anti-Tuberculosis League, Fort San, Saskatchewan.

cient similarity to the foregoing to be accepted as instances of the condition.

In view of the widespread use of artificial pneumothorax in the treatment of pulmonary tuberculosis, the frequency with which this condition occurs is of interest. No statistics could be found in the available literature other than that of Reyer and Kohl's 10 cases which occurred in a "series of many thousand insufflations during the course of about four years."

In this institution artificial pneumothorax was first given in May, 1919, and, to the end of 1929, 7,782 refills had been given to about 300 different patients and 163 unsuccessful attempts were made, in 103 of which air was actually introduced within the chest. During the same period we have record of 583 chest punctures for exploration, aspiration or irrigation, in 200 of which the withdrawn fluid was replaced with air. One closed drainage was carried out and nine rib-resections were done. No thoracoplastic collapses were done within the institution. This makes a total of 8,528 needle punctures of the chest, in 8,085 of which air was actually introduced. It would be interesting to know in how many of these the needle pierced the visceral pleura and was within the lung tissue but such figures are impossible to obtain.

With this amount of pneumothorax experience we have had 6 cases in which alarming symptoms developed suddenly during the administration of the treatment. One was classed as a reaction to novocaine as the parietal pleura was not pierced; two appeared to be attacks of syncope; one seemed to be due to extreme nervousness; two, one of which was fatal, were classed as pleural shock at the time, but on review might have been due to cerebral air embolism. Complete details of these occurrences were unfortunately not recorded.

The writers here quoted believe that many cases previously considered pleural shock were more probably due to air embolism, and in this connection it is interesting to note that Rubstinat and LeCount (4) discuss the possibility of coronary air embolism being responsible for the sudden reactions occurring during thoracic operations or injuries.

Case Report

G. S., male, aged 29, Roumanian, was admitted to the Sanatorium January 30, 1926, with a diagnosis of pulmonary tuberculosis involving chiefly the right lung. Roentgenograms showed in this lung dense parenchymatous tuberculosis throughout the upper half with less dense disease in the remainder, and,

in the left lung, tuberculosis of the upper lobe showing considerable evidence of fibrosis. Sputum was positive for tubercle bacilli (Gaffky IV). Temperature was 99.5° in the evening and pulse 88 to 100.

Pneumothorax collapse of the right lung was advised, and the initial insufflation of 400 cc. of air was given on February 8, 1926. Partial collapse only was secured, the lung above the level of the second rib being adherent to the chest-wall. Effusion developed in September, 1926, which persisted in varying amounts as long as the pneumothorax existed. Seven aspirations were done, the fluid being replaced with air and pneumothorax continued.

By October, 1928, the patient had gained considerably in weight and his general condition was much improved. Temperature was rarely over 99° and pulse 90. After the appearance of fluid the usual refill was 100 cc. given every two weeks, and terminal pressures of about plus 60, plus 80, were recorded. (Readings in millimetres and of one arm of manometer; that is, one-half of the true pressure.) These positive pressures were continued in an effort to maintain the pneumothorax as the collapse was gradually decreasing. The patient was totally in bed until March, 1927; then on exercise to bathroom once daily until November of the same year when he was given full bathroom exercise.

On October 6 and 11 four attempts to enter the pleural cavity failed. This was by the same operator as before. Ninety-six refills had been given to date. On October 13, 150 cc. of air were introduced; initial pressure minus 10, minus 20, and terminal, plus 20, plus 20. That night the patient's temperature was 101°, and he complained of pain in the right side of the chest. This condition rapidly subsided.

On November 3, following the usual fluoroscopic examination it was decided to try puncture in a new area further to the front. A point was selected in the sixth interspace in the anterior axillary line and, after infiltrating the skin, the needle was inserted. When the point was well in between the ribs the plunger of the piston could be drawn up and down fairly freely, and it was thought that the needle was in the pleural cavity. A little colorless froth appeared in the bottom of the syringe. The manometer connection was made and a reading of minus 10, plus 10, was taken. The needle was thought to be in a bronchus. It was withdrawn slightly and a reading of minus 15, plus 5, obtained, which was presumed to be the pleural cavity as these figures had been common initial readings. Air was let flow in, and the patient immediately commenced to bring his arm down over the site of puncture. The air was shut off at once and the needle whipped out. At the most, only 25 cc. of air could have entered the chest.

The patient held himself rigid, was slightly cyanosed, had a staring expression with eyes fixed, and answered questions very slowly and in a whisper. Pulse and respiration were good. Pupils were slightly contracted and equal. His head was raised and he was given brandy. This was followed in a few minutes

by a hypodermic of 1/30 gr. of strychnine. He now attempted to sit up but was held back. His condition remained unchanged for a few minutes and then clonic convulsions of the right arm occurred. They would last a few seconds and be repeated in half a minute or so. It was now noticed that the left arm and leg were flaccid. There was a suggestion of paralysis of the left side of the face. He began to shiver, and drops of perspiration appeared around the lips and on the forehead. He yawned prodigiously several times, and had an attack of hiccoughs. Moderate pallor was now present and the pupils were slightly dilated and equal. There was no deviation of the eyes noted. Unfortunately no ophthalmoscopic examination of the retina was made.

He was removed to bed, the foot elevated, and warm blankets and hot water bottles applied. The churning "millwheel" murmur, indicative of air in the cardiac cavities, mentioned by some writers, could not be heard. The convulsions of the right arm recurred with increasing intensity and frequency; the right leg was not involved. The left arm remained flaccid and there was some movement of the left thigh. Left-sided facial paralysis was now fully developed, and the eyes deviated to the left. There was no sensory disturbance elicited. On being questioned, the patient complained of being cold and was perspiring freely. He also complained of severe right-sided headache. During this time he was only partially conscious, articulated poorly, and answered questions haltingly. The pulse was good and the respirations somewhat irregular.

The patient remained like this for about two hours and the convulsions gradually became less frequent; he vomited and after this seemed brighter. He could talk in about his usual manner, and the facial paralysis had disappeared. In about an hour he became very drowsy and could hardly be roused. Pulse and respirations continued good. He lay on his right side with head pulled over in this direction. The clonic contractions occurred now only after some irritation or movement. Taking the pulse would bring on a slight attack. There was some twitching in the left arm. Knee jerk, plantar and biceps reflexes were normal at this time. Blood pressure, lying, was 128–76.

Six hours after the attempted pneumothorax he was again mentally alert but complained of more generalized headache. He could now move the fingers of the left hand. The contractions had entirely ceased. Temperature was 99° at 7 P.M., and pulse 120.

He slept throughout most of the night. In the morning the headache was still present and there was more movement in the fingers. By the second morning movement was completely restored, although the patient complained of a tingling sensation in the fingers. The grip of the two hands was practically equal. The headache had entirely disappeared and appetite was normal, and the patient appeared none the worse for his experience.

He stated that he had felt nauseated before going up to the operating room

and that this increased after getting on the table. He was not conscious of any pain with the insertion of the needle or the introduction of air. He remembered suddenly feeling very cold. He could not recall any pain at site of puncture. The only other thing he could remember was being told to lie back and not to try to sit up. Memory was a blank for the next two or three hours. For some time after this he could see double and remembers the sensation of cold, almost like "freezing" as he put it.

Attempts to continue pneumothorax were not repeated and the patient was discharged in January, 1929, as "Improved."

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INSOMNIA IN TUBERCULOSIS

W. C. SERVICE[1]

One of the most exacting and trying problems that confronts the physician caring for tuberculosis cases is insomnia and its complicating phenomena. In reviewing the literature on insomnia, one finds that the theories that were in vogue three or four decades ago have changed very slightly since that time. As pointed out by Kingman (1), insomnia is an inevitable by-product of our modern high-pressure manner of living. Its increase has been proportional to the movement of population from rural to urban surroundings, and to the growing preponderance of mental over physical labor.

Modern civilization has produced changes in living conditions so that, after a full day's work, an individual is enabled by modern invention to enjoy another day of recreation which his forebears spent in relaxation or sleep. To-day when the individual normally begins to relax and perhaps feel drowsy about 9 P.M. he fights off this sensation and plans for an evening of recreation. He is stimulated to false energy as the hours pass and when he finally does retire he is often desperately wideawake.

Insomniacs of this type frequently state that they have been able to sleep only two or three hours at night for weeks, months, or even years. Regardless of the actual time they sleep, fear and apprehension remove all the natural satisfaction that should be associated with sleep and the insomniac awakes in the morning, tired and lacking in energy and enthusiasm for the day's work. He is fatigued both mentally and physically on arising and finds it difficult to concentrate on his problems. As the day passes his energy gradually returns, but it is usually late in the afternoon before his normal vigor is resumed. By evening his energy has fully returned, he is wide awake and without the slightest desire to sleep, and so a vicious cycle is started. The tuberculous individual frequently experiences this type of reaction preceding a "break."

NORMAL SLEEP

The most striking and important fact, in normal sleep, is the partial or complete loss of consciousness due undoubtedly to the lessened activity

[1] The Colorado Foundation for Research in Tuberculosis, Colorado Springs, Colorado.

of the brain tissues, particularly of the cortex cerebri. Following relaxation, the power to make conscious movements is first lost and then the use of the special senses disappears. The first of these to go is vision and the last hearing. During sleep the most easily aroused sense is hearing, while the senses of touch, taste and smell are progressively more difficult to excite. During deep sleep all voluntary muscles are relaxed, respiration becomes deeper and slower and tends to rise and fall as in Cheyne-Stokes breathing. The pulse frequency is lessened, the blood-pressure falls, the temperature is lower, and the secretion of tears, mucus and urine is diminished. There is general inactivity of the cerebral cortex.

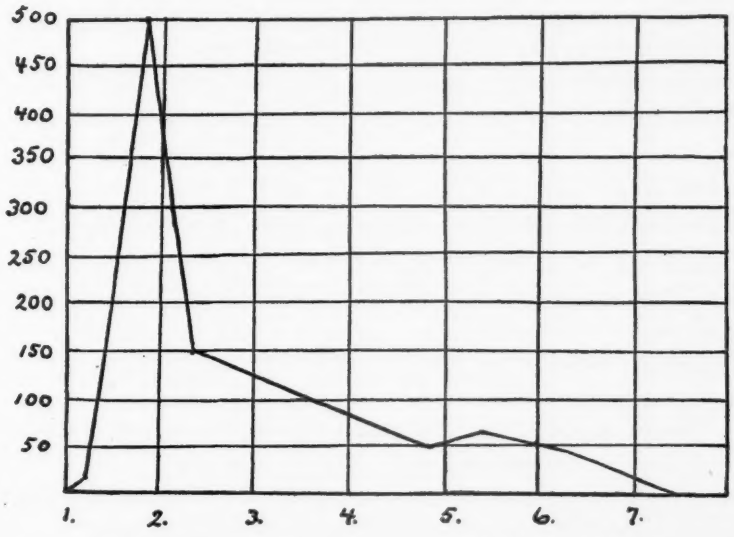

CHART 1. CURVE OF INTENSITY OF SLEEP ACCORDING TO MONNINGHOFF AND PIESBERGEN

The figures along the ordinate show the relative intensity of sleep, measured in milligram-millimetres, expressing the intensity of the sound caused by a falling body necessary to awaken the sleeper. (Modified from Howell's *Textbook of Physiology*.)

As pointed out by Callender (2), a very important point in normal sleep is the variation in intensity, which has been investigated by a great many observers, among whom may be mentioned Kohlschutter, Czerny, Howell and Michelson. It was found that there was a rapid increase in the intensity of sleep during the first two hours of slumber, which reached its highest point between the first and second hours, and dropped very rapidly again, so that by the third hour the sleeper was very near the margin of consciousness. From that point on the depth of sleep became less until waking occurred.

The periodical occurrence of sleep would appear to be due to fatigue of, and therefore lessened activity of, the vasomotor centre in the medulla, brought about by its continuous activity during the waking hours. Anything that tends to upset the fine adjustment of blood distribution may give rise to insomnia.

INSOMNIA

Insomnia is the inability to secure a sufficiency of normal physiological sleep under favorable external conditions. A sufficiency of physiological sleep denotes that amount which is sound, restful and usual for a particular individual, although the actual duration and depth of sleep may vary with the individual's age and personal constitution.

From an aetiological standpoint the main factors responsible for insomnia, in the tuberculous individual, may be classified as follows:

A: Physiogenic Causes

Insomnia resulting from physical discomfort or organic disease.

1. Pain: pleurisy, neuralgia, adhesions.
2. Dyspnoea: advanced phthisis, hay fever, asthma, nasal obstruction.
3. Cough: irritation of any part of the respiratory tract.
4. Pyrexia: toxaemia, colds.
5. Gastrointestinal disturbances: pain, flatulence, palpitation.
6. Toxic states: restlessness, twitching, tremors.
7. Circulatory disturbances: elevated blood-pressure, cold feet.
8. Frequency of micturition: irritation of urinary tract.
9. Pruritis: skin diseases.
10. Organic cerebral disease: meningitis.

B: Psychogenic Causes

Insomnia in which no definite physical basis is found.

1. Anxiety states: mental conflicts, complexes, disturbing dreams.
2. Neurasthenia: states of fatigue, physical or mental, due to slight exertion.
3. Hysteria: autosuggestion.
4. Confusional states: delirium.
5. Compulsion neuroses: obsessions.

EXPERIMENTAL INSOMNIA

Recent studies on exhaustion due to lack of sleep by Leake, Grab and Senn (3) showed that rabbits, subjected to stimulation in revolving cages to prevent sleep and in which the fatigue factor from exertion was reduced to a minimum by forcing the rabbits to change position only eight times per minute, could be fatigued to the point of collapse and even death. There was considerable individual variation, the collapse coming on in some after seven days while in others up to thirty-one days.

Bast and Bloemendal (4) observed that in rabbits, exhausted after several days from lack of sleep, the degree of chromatolysis in the cells of the medulla was more marked than in the cells of the spinal cord, although the cells of the reticular formation also showed changes. The somatic motor cells in the somatic motor column of the anterior horn and the cells of the hypoglossal nucleus underwent little or no change as the result of exhaustion by sleeplessness.

TYPE OF INSOMNIA

It is probable, indeed, that no true primary insomnia ever occurs, and in dealing with any case of insomnia it is essential to regard the sleeplessness as a symptom and to use every endeavor to ascertain the exact nature of the underlying disturbance. It is well never to accept a complaint of insomnia without investigation, but it is just as foolhardy to ignore this complaint.

Five general types of insomnia may be easily recognized:

1: Complete absence of sleep.
2: Sleep on retiring for two or three hours and then wakefulness for the remainder of the night.
3: Wakefulness for two hours or longer on retiring and finally sleep.
4: Wakefulness on retiring, sleep for two or three hours, and then wakefulness the remainder of the night.
5: Dreams: disturbed or restless sleep.

The first class is probably never seen as a primary condition. In tuberculosis it is most commonly seen during a miliary or an acute toxic phase of the disease when the patient has an elevation of temperature and the progress of the disease has not been checked. Often in the acute, far-advanced stages of tuberculosis, patients who have been unable to sleep will sleep or doze most of the time. The toxaemia at this stage has become so profound that the patient sleeps because the centres in

the brain have become so affected that their functioning is impaired. Complete insomnia fortunately is usually of short duration, as complete rest tends to lessen the toxaemia and partial insomnia or even natural sleep follows. This first type of insomnia is commonly seen in acute disease regardless of the nervous constitution of the patient.

Case 1: F.M.S., white, male, age 31. Diagnosis of tuberculosis first made in July, 1927. Moderately advanced lesion of both lungs. Was a sanatorium patient in one of the central states for a year. His condition failed to improve and he came to Colorado. During the next year both lungs cleared considerably, and for the next six months he was up to meals and spent some time in a chair in the mornings. His case was apparently progressing favorably when he contracted a severe cold and had an exacerbation of his tuberculosis. The patient had been sleeping well until this time. When he learned that his tuberculosis had broken down in one area, he immediately began to fear he was going to die and began to have severe insomnia. Fear and apprehension soon destroyed all desire for sleep and complete insomnia developed. The insomnia was disregarded and he was told he didn't need much sleep since he was resting in bed all the time, and the rest would do him as much good as the sleep. His physical condition and his insomnia did not improve, and he finally became almost maniacal. A neurologist was called in consultation and advised the use of sedatives; large doses were necessary since his insomnia had been permitted to progress so far. These gave him some of the needed rest and he gradually began to rest and feel better. He tried omitting them after a few days, but his insomnia returned as severe as at first. He then tried for a period a gradual reduction of his dosage, and this combined with psychotherapy resulted in his getting control of his mental state, and his insomnia improved. At present he is not using any drugs. He has recently attempted to apply progressive relaxation with apparently very favorable results.

The second type of insomnia is perhaps most commonly seen in cases having moderate toxaemia. During their waking hours the patients become fatigued sufficiently to sleep on retiring. Usually these patients obtain a very profound sleep for the first two hours, which is followed by a sharp return to the near-conscious state. At that time the tuberculous toxaemia is sufficient to alter the threshold of the various cortical centres, so that they awaken suddenly. There is usually no period of drowsiness supervening; rather they awaken startled, all senses alert, and with not the slightest desire for sleep. Many of these patients lie awake and with their minds active until near morning, when they sometimes drop into a short sleep from fatigue. Patients of this type usually feel rather

stimulated during the morning hours, but become quite fatigued as the afternoon passes.

Case 2: White, male, age 29, electrician. Diagnosis of tuberculosis made three months previous to hospitalization. Previous to diagnosis the patient had felt unduly tired after working for about two years. He contracted a cold and developed a pleurisy during this time. He was found to have a moderately advanced case of tuberculosis of the right lung. Following hospitalization intestinal tuberculosis was diagnosed by X-ray. Highest temperature 98.8°, pulse 90. The patient was confined to bed, and ultraviolet radiation given for the intestinal condition. For a month previous to hospitalization he had been experiencing restless nights and these gradually became more frequent. At the time of admission he had no difficulty in going to sleep, but he would awaken usually about three hours after retiring, occasionally sleeping as much as four hours. He would always awaken suddenly and there was never any feeling of drowsiness. He would remain awake then until morning, by which time he always felt very tired and restless from his efforts at trying to sleep. He did not doze or sleep during the day. On a few occasions, when he would awaken within an hour or hour and a half after retiring, he would drop into a short sleep near morning for an hour or two. This condition persisted about four months without any improvement. He was discharged from the sanatorium after nine months, at which time he was getting almost six hours sleep at night. He cured for a year outside a sanatorium; at the end of this time he was sleeping normally and returned to work.

Cases of the third type of which the patients lie awake for hours before being able to go to sleep are usually the ones who have developed mental conflicts, especially that of fear. These cases, under the guidance of a kind understanding physician, who has a knowledge of the psychological problems of this type of patient, do extremely well. Fear intensifies a condition of insomnia and its removal may produce a cure. Fear is an emotion; an emotion is the determining factor of a complex; a complex is an essential part of a conflict; and either a complex or a conflict is in itself quite capable of producing insomnia. A complex is an idea plus an emotion. When one complex meets another that is opposed to it a conflict results.

In the case of a man whose insomnia is complicated with a fear neurosis, we find the following process going on. If his sleeplessness is of long duration, he begins to think of sleep when he starts for bed or long before. To this simple thought of sleep there is immediately added the complicating emotion of desire. Instead of thinking of bed, going to bed and going

to sleep, the patient gets upset by thinking how much he would like to sleep and how delighted he would be if he could only sleep. Thus we have the first element of a conflict, a simple idea of sleep plus the complicating emotion of desire, and hence a complex. When he starts to undress, the patient says to himself, "I am afraid I am going to stay awake to-night as usual." Here is the other element of the conflict, the idea of wakefulness plus the complicating emotion of fear. The conflict is one between sleep and desire, on the one hand, and wakefulness and fear on the other.

Case 3: F.H.G., white, female, age 25. Patient experienced cough and loss of weight for about three months previous to diagnosis of tuberculosis. Examination revealed a minimal case at the left apex. The patient was of emotional type and was very restless. Bed-rest was maintained with difficulty, and she worried considerably about her condition as she continued to lose weight. Financial worries augmented her difficulties, and she began to find it difficult to go to sleep at night due to excessive mental activity. Physical examinations and X-ray films showed that her condition was improving, but she had no faith in the reports as she felt badly and she continued to get less and less sleep. She would usually lie awake until 2 or 3 A.M., and then sleep until near six. The loss of sleep produced anorexia and finally severe nervous indigestion; as a result she continued to lose more weight. Reasoning with her about her condition was absolutely without result unless for the worse. She was finally given hypnotics and as she began to sleep more her physical and mental condition improved. At present she is attempting progressive relaxation and this, with the help of hypnotics occasionally, is showing good results, as she has gained seven pounds in the past three weeks and feels much improved physically.

Patients whose symptoms conform to the fourth group are combinations of the second and third groups. Their inability to sleep on retiring is due to the development of a fear complex or conflict. The inability to stay asleep may be partly due to the neurosis, or in part, or entirely, to the previous damaging effects of the tuberculous toxin. Clinically it seems that practically all patients have a more unstable and irritable nervous system during and after recovery from tuberculosis than they had before the disease developed. This may be manifested in a great variety of ways, but chronic insomnia is one for which the patient usually seeks relief.

Case 4: White, male, age 27. Patient experienced a slight cough and moderate fatigue for almost a year previous to the onset of his tuberculosis, which

was with a small haemorrhage. Four months previous to onset he had begun to have restless nights, having some difficulty in going to sleep but greater difficulty in staying asleep. At first he would awaken about 3 A.M., and then doze and awaken frequently until morning. About two weeks previous to haemorrhage he began to sleep much worse and had a rather marked anorexia. He slept well for three nights following the haemorrhage and dozed a great part of the day. Forced feedings were started and his anorexia became very severe and there was occasional vomiting. He entered an eastern sanatorium, where his condition was diagnosed as a minimal case with involvement of the left apex. His highest temperature was 98.8° and pulse 82. After two weeks he was permitted up for meals and exercise was started in another two weeks. His insomnia had returned after the first few days and the anorexia had become very distressing. Various medications, including all the tonics and wines, were given for the nausea and vomiting, but nothing for the insomnia, both of which persisted and continued to grow worse. The continual gastric distress started the patient worrying about his condition, and he began to fear he was losing ground, which soon resulted in his having greater difficulty in going to sleep. He was discharged from the sanatorium after six months as a quiescent case, although his insomnia and his gastric distress had not improved, and two days later he began to bleed. He became a bed patient at his home, where for the next seven months, during which time he had intermittent blood-streaked sputum and haemorrhages, the insomnia, anorexia and vomiting continued. Finally hypnotics were administered, and the insomnia and anorexia improved and the vomiting ceased altogether. He has continued to use hypnotics for a year and a half and now gets about seven hours sleep at night. After carefully regulating his dosage and changing from one type of hypnotic to another every few days, he has been able to keep from ever increasing his dosage. He is now decreasing the use of the drugs, and for the past few months he has been doing a half-day's work.

The last group of patients usually complain of having a "restless night." Their sleep may be broken by dreams, or they may complain of becoming tired in one position, and the frequent changing of position may not give them the restful sleep they desire. The heightened irritability of their nervous centres brings their threshold of sleep very near their threshold of consciousness and it consequently takes only the slightest stimulation to arouse them.

Case 5: White, female, age 26. Onset of tuberculosis was with cough and expectoration following an attack of influenza. After the influenza she did not seem to regain her strength, and for a month before the tuberculosis was diagnosed she had had what she describes as restless nights. She would awaken

frequently, and always felt very tired on arising in the mornings. Sometimes she would have very terrifying dreams from which she would awaken very nervous. The dreams seemed to become more persistent, and she awakened so frequently that the loss of sleep was lowering her general physical condition. She was diagnosed as a moderately advanced case of tuberculosis and was confined strictly to bed for three months. By the end of the first month she was much improved and was sleeping almost normally.

EFFECTS OF INSOMNIA

The effects of insomnia are not visited upon any certain part of the body but upon it as a whole. Some parts seem to be affected more than others, but this probably depends upon constitutional differences of the individual.

Following a few restless nights or nights of partial or complete insomnia the first symptom observed by others rather than the patient is the tendency of the individual to complain and to be more irritable than usual. General restlessness is increased, and the patients find it difficult to lie in bed. There may be a feeling of general lassitude but the nervous irritability prevents relaxation. There is usually a tired feeling about the eyes and a sense of muscle-strain. After several days of prolonged restlessness and insomnia the patients feel extremely tired and depressed on arising, or, provided they have dozed for a short time previous to their usual time of arising, they may feel refreshed for a few hours and the lassitude and weariness develop as the day progresses. They usually complain frequently and about seemingly trivial matters, and it is quite usual for the attending physician to say that they are of the very "emotional type" and easily upset, or are neurotic, and unfortunately dismiss their complaints on these grounds.

Headaches are particularly prone to develop in the afternoon, along with sweating, clammy hands, cold feet and other vasomotor disturbances. The eyes may feel particularly fatigued and the eyeballs frequently ache. These things all work to prevent resting during the day as well as at night. Patients who read often complain that they feel they are losing their mental grip. They read and it becomes a process of merely observing words, and they cannot tell what they have read a short time later. In the more prolonged insomnias there is a complete loss of vigor and all vital energy seems to be lacking. Fear and worry complicate the picture and the patient soon finds himself on the road to a relapse.

Temperature: Fever is usually one of the earliest signs of activity and

is due to the effect of the tuberculotoxin on the heat-centres. Anything that stimulates the lymph- and blood-flow favors the discharge of toxins which produce fever. A patient at rest may be afebrile, but most clinicians have observed rises in temperature following emotional states from seemingly trivial causes. In cases of insomnia the hourly temperature curve usually is above the normal curve for that individual, and the evening and early morning temperatures do not fall as soon or as low, due to the nervous hypertension. The previously afebrile case may show an elevated temperature of from 0.2° to a degree. Osler (5) states that the temperature of consumptives is very easily influenced by apparently trivial causes which would not affect the normal person, and he mentions excitation in particular.

Pulse: The pulse in tuberculosis is increased in frequency and usually in proportion to the temperature. In men it has been observed that an increased pulse-rate may more often be an indication of activity than is ordinarily considered, and an increased pulse-rate may be observed more frequently without an elevation of temperature in men than in women (6). In insomniacs the pulse-rate is usually increased from ten to fifteen beats per minute over the individual's normal range. A vicious cycle is thus established when the pulse-rate is increased, and this in turn favors the increase in toxic output from the focus of infection.

Gastrointestinal: Perhaps the most distressing effects of insomnia for the patient are the gastrointestinal symptoms. At first the food may seem to have lost its flavor and aroma, but gradually the desire for food is lost. The anorexia often becomes so marked that there may be positive loathing for food and a dread for meal time to come. The sight, or often even the thought, of food produces a most distressing nausea and every morsel swallowed is torture. Nausea of this type is not relieved by the usual medications that are given, but it is frequently made worse. The nausea may sometimes be relieved by vomiting, but more often it is quite distressing for two or three hours and then it gradually subsides but never entirely disappears. Highly seasoned foods seem to provoke greater distress than others. Patients sometimes state that they could eat if they could only swallow the food after chewing. Liquid foods are most easily partaken and unless the insomnia is relieved an almost wholly liquid diet is resorted to for relief. This is purely a nervous indigestion and has been excellently described by Alvarez (7), who discusses the use of psychotherapy, sedatives and hypnotics, and diets in these cases. There may be considerable formation of gas in the stomach. Constipa-

tion or diarrhoea may be present, and I have observed in a few instances a decreased or total absence of hydrochloric acid in these very nervous and nauseated cases, the acid secretion returning after the symptoms have been relieved.

TREATMENT

The treatment of insomnia first resolves itself into an accurate diagnosis of the condition producing the insomnia. When it is due to one of the physiogenic causes, a simple correcting of this, if possible, may eliminate the insomnia. Perhaps most cases will demand a systematic study and the carrying out of a rather complicated program of treatment, which should be only in the hands of a sympathetic and understanding physician.

Rest: The patient in bed is not necessarily at rest. The amount of activity necessary to produce fatigue or marked changes in the pulse, temperature, respiration and other reflex activities, varies with each individual. At times an increment of activity may produce results that ordinarily would be considered slight; such an increment at other times would be considered excessive exercise. Reading a novel may prove very trying to a patient with fever. The general state of the individual as well as the character of the activity determines whether it should be considered excessive. During fatigue or high fever all unrequired activities, voluntary or involuntary, should be termed excessive.

The patient advised to remain in bed often fails to secure the desired results because he may not know how to relax; also, the restlessness may be increased by distress over his condition. The result is that he tosses in bed, lies stiffly, or is uncomfortable, and the purpose in prescribing rest is nullified. Since rest is so evidently essential, the most scientific means of obtaining it should be used.

Progressive Relaxation: Jacobson (8) observed that an individual might lie in bed apparently quiet for hours and yet remain sleepless and nervously restless. Various external objective signs and tests indicated that rest was not complete, and accounted for the patient not feeling refreshed after resting. This so called "residual tension" is always present in insomnia and can be relieved if the fine tonic contraction of the muscles is overcome. Accordingly, if the patient becomes able to relax the voluntary system there later tends to follow a similar quiescence of the involuntary system. The method of progressive relaxation may be used along with psychotherapy, sedatives, or other forms of therapy

when therapeutic results are desired, and the scientific evaluation of any one particular method is not desired. A complete study of the methods of progressive relaxation is given in the *University of Chicago Monograph in Medicine* on *Progressive Relaxation* by Jacobson. A thorough study of methods and their application should be made by every physician attempting to treat insomnia.

Hypnotics and Sedatives: This is probably the most neglected, as well as misused form of therapy. A great proportion of the medical profession, as well as the lay public, still believe a sleeping draught means morphine in some form. Morphine is a good pain reliever but a poor sleep producer. As Alvarez (7) says, "Time and time again I have brought a nervous patient almost back to health and full time work, only to see him plunged back into insomnia and despair by the angry protests of some medical friend of the family who raged about 'weak kneed dope fiends,' and prophesied disaster."

Several somnifacients have been tried and all those discussed have certain advantages under given conditions. In working with these drugs a method of administration was developed whereby it appears to be possible to give these hypnotics over a period of years, if necessary, without increasing the dosage of the drug. Four drugs are selected, such as paraldehyde, diallylmalonylurea (dial), alpha monobromisovalerylcarbamide (bromural), and isoamylethylbarbituric acid (amytal). The approximate equivalents of each were determined, which were that 2.5 cc. paraldehyde equals about 1.5 grains of amytal or 10 grains of bromural or 1.5 grains of dial. Each drug is taken for about three times in succession and then another is taken until all four have been used; then the process is repeated indefinitely. By this method a variety is obtained and the individual apparently can continue the use of hypnotics without becoming more tolerant to any of them. Following is a list of hypnotics that have been tried and their advantages and disadvantages noted:

1: Sodium isoamylethylbarbiturate (*sodium amytal*). In cases of complete insomnia, when the patient is so upset and nervously stimulated that even large doses of hypnotics orally have but a moderate effect, the use of this drug produces an almost immediate sleep. By repeating the drug for a few successive nights the patient is in such an improved mental and physical state that the use of smaller doses of drugs orally will give the desired results. It is especially indicated in those cases that become almost maniacal from loss of sleep. Its chief disadvantage is that it must be freshly prepared to maintain a pH concentration of around 9.6 for the

best results. Also, the intravenous administration is a disadvantage under certain occasions.

2: Isoamylethylbarbituric acid (*amytal*). This is one of the best of the stronger hypnotics. For the moderate case one or two tablets (1.5–3 grains) is sufficient. A very restful sleep is produced without undesirable effect the following day. The drug can be given for a considerable time without its being necessary to increase the dosage. Occasionally some patients complain of being more nervous for a short time after taking the drug, but this is usually from having overexerted just previous to retiring.

3: Diallylmalonylurea (*dial*). This has proved to be a very effective hypnotic. It seems to act somewhat more rapidly than most hypnotics, and its action is prolonged, so that the patient receives a restful night's sleep. There is a slight tendency to drowsiness upon awakening but no unpleasant sensations.

4: Calcium ethylisopropylbarbiturate (*ipral*). This is one of the stronger hypnotics and is effective in small doses. In so far as it has been used, there appears to be very little tendency for any tolerance to develop. One case gives the history of taking it for over two years and has only increased his dosage to four grains. Occasionally some patients will notice that they are made more irritable for a short time after taking the drug.

5: Alpha-monobromisovalerylcarbamide (*bromural*). This is one of the milder and more slowly acting hypnotics. Usually doses of about ten or fifteen grains are needed for the moderate case of insomnia. The effect is usually not as prolonged as in the case of the stronger drugs. It is an excellent drug to use in reducing dosage preparing for the cessation of the use of drugs.

6: Bromdiethylacetylcarbamide (*adalin*). This drug is very similar in its action and uses to the drug described above.

7: Paraldehyde. This is a very effective hypnotic in liquid form. It has been particularly used in those cases in which a neurosis is predominant and prevents sleep on retiring. This drug produces a benumbing effect which is quickly followed by relaxation and sleep. Its greatest disadvantage is its disagreeable taste.

Aids: In order to promote sleep and relaxation, prolonged tepid baths have been employed, particularly in a few sanatoria. General massage or alcohol back-rubs upon retiring benefit a great many nervous patients. Warm or hot drinks given at bedtime seem to have a soothing effect in

many cases. Patients who are awakened by the light in the mornings may get relief by wearing a black eye-mask. Every practitioner has had occasion to quiet some patient by removing irritants, or by using soothing tones and reassurance or the inspiration of confidence. A diet low in proteins may in some cases prove beneficial. Fresh air has often proved a simple and very useful remedy. In addition to the rest cure, hypnotics, progressive relaxation, it is usually admitted that a few other remedies, such as bromides and other sedatives, suggestion, persuasion, hypnotism, and perhaps the analysis of Freud, are useful in their place, but limitations and objections are common, and the gap in therapy is apparent.

COMMENT

Tuberculous infection brings about usually a condition of nervous hypertension which is characterized by a condition of hyperexcitation and hyperirritation. A myriad of theories have been advanced as to the causes of this nervous hypertension by Meynert (9), Kraft-Ebing (10), Löwenfeld (11), Binswanger (12), Goldscheider (13), and many others, but after careful investigation of all the proposed theories nothing definite has been established as to how much is due to toxaemia, to habit and impulse resulting from past experience of pain and suffering or fear, or to congenital or other factors.

The exciting causes are too varied and numerous to list, but vary from the most acute to the most chronic causes. Fear, worry, pain, vasomotor disturbances, and toxaemia are far the most common.

The clinical manifestations of nervous hypertension may also be classified according to that portion of the nervous system involved. Many researches have been devoted to determine the effect of tuberculotoxin upon the sympathetic and vegetative nervous systems, but as yet nothing of definite benefit has been learned.

Nervous hypertension may precede tuberculosis as a whole or as part of the exciting cause, or it may be manifested during the course of the disease. Its symptoms may then be the result of the action on the nervous system of toxic, bacterial, nutritional or other factors responsible for the disease, but often they are reflex actions to sources of pain, anxiety, discomfort or fear.

During severe acute tuberculosis, nervous hypertension is commonly seen in the form of restlessness, insomnia, or even delirium. Apparent inability of the patient to lie quietly sometimes seems to prevent

recuperation. Individuals who during ordinary life are described as "nervous" are particularly likely to show hyperactive symptoms.

Various objective and subjective symptoms may be increased in those patients inclined to worry. Cough, if present, may occur upon very slight provocation, often becoming almost paroxysmal and with very little expectoration. Palpitation or increased pulse-rate disproportionate to the fever, if present, is frequently observed. Almost everyone has observed increases in temperature due to even slight excitement, nervousness or worry. Following a haemorrhage, a patient frequently becomes so nervous and excitable that marked rises of temperature and pulse occur which often help to bring about further haemorrhage. The elevation of temperature in insomnia may be only a tenth of a degree or as much as a degree. When the nervous system is quieted this elevation of temperature subsides.

In convalescence when the physician's attention is less engrossed with the acute phases of the disease, the nervous manifestations become more conspicuous, and, unless measures have been taken to alleviate the psychic factor, these after-effects may become more troublesome than the acute stage of the disease. The restlessness and complaining of insomnia may become so marked as to interfere with recovery from the disease, and then also the gastrointestinal symptoms, nausea, anorexia, dizziness, belching, vomiting, flatulence and diarrhoea may arise of nervous origin. McLester (14), in a series of approximately 1,600 cases complaining of gastrointestinal disorders, determined that at least a third of the patients who come to the consultant with these complaints are psychoneurotic. In tuberculosis sanatoria, gastrointestinal complaints are extremely frequent. These complaints are almost invariably associated with insomnia or nervousness in some form. In most cases treatment is confined to the gastrointestinal tract rather than treating the nervous origin which should be the basis of treatment. Each case demands careful individual treatment, in which psychotherapy, progressive relaxation, hypnotics and other aids all have their special function to perform.

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RACIAL TUBERCULOSIS IN SYRIA

(Second communication[1])

RAYMOND H. GOODALE

A previous communication (1) dealt with tuberculosis in Syria as revealed by the intracutaneous tuberculin test carried out on 1200 Syrians and Armenians. It is the object of this paper to discuss the clinical tuberculous cases admitted to the American University Hospital from 1908 to 1929 inclusive. Since Syrians and Armenians make up most of the permanent population, only these two races were included in the total of 1150 patients. Most of these patients came from cities and mountain villages along the coast. There is a roving population of about 200,000 Bedouin Arabs in the Syrian Desert of whose diseases we know very little at present.

Syria is a French mandate lying along the eastern coast of the Mediterranean Sea. Beirut, the largest seaport of Syria, is the gateway to the Near East. For this reason there is a great deal of commerce which brings travelers from Europe and America, especially in recent years. Thus Syria has become exposed to tuberculosis and other occidental diseases. Another source of tuberculosis has been found in Syrians who have returned to their homeland to pass the rest of their lives. Many of these, having resided in foreign countries, have contracted the disease and have spread it among their countrymen.

In America we have been fortunate in developing something of a racial immunity, which in combination with our sanatorium isolation of tuberculosis has progressively decreased our death-rate. We can hardly realize, therefore, with what horror tuberculous inhabitants of a village are regarded in certain parts of Syria. They are shunned much as we would shun a leper, and in the past they have been stoned and driven from their homes. Introduction of sanatorium treatment has changed this attitude especially in the coast cities. But tuberculosis still lives up to its name of the "white plague" in the interior where the people are not tuberculized and have acquired no immunity.

[1] From the Departments of Pathology of American University of Beirut, Syria, and of the City Hospital, Worcester, Massachusetts.

The data for this article were taken from the hospital records. A few cases of questionable diagnosis were excluded. The cases of tuberculosis of other races than Syrian and Armenian were also excluded.

The first fact which attracts attention is the preponderance of nonpulmonary over pulmonary tuberculosis, especially among the Syrians. Reference to table 1 shows 66.4 per cent nonpulmonary as against 33.6 per cent pulmonary among Syrians. The difference is not so marked among the Armenians,—53.8 per cent nonpulmonary and 46.2 per cent pulmonary. The difference in numbers by age-groups among Syrians in these two general groups of tuberculosis is readily seen in chart 1. The number of nonpulmonary cases is much higher except in the 40–49-year group. It is interesting to compare these figures with those obtained by analyzing a group of 838 cases admitted to the Worcester

TABLE 1

General distribution of tuberculosis

	SYRIAN MALES	SYRIAN FEMALES	TOTAL SYRIANS	ARMENIAN MALES	ARMENIAN FEMALES	TOTAL ARMENIANS	GRAND TOTAL
Pulmonary	184 36.1%	136 30.7%	320 33.6%	48 44%	44 48.8%	92 46.2%	412 35.8%
Nonpulmonary	325 63.9%	306 69.3%	631 66.4%	61 56%	46 51.2%	107 53.8%	738 64.2%
Total	509	442	951	109	90	199	1,150

City Hospital during the past ten years. Of these, 386, or 46 per cent, were nonpulmonary, and 452, or 54 per cent, were pulmonary. Such figures, showing a higher percentage of pulmonary cases, are to be expected in America, which is more highly tuberculized. Syria is a relatively nontuberculized country, judging by the results obtained in a previous article (1). There was an average of 42 per cent positive tuberculin tests for all ages among both Syrians and Armenians. One group of 94 Syrian boys in a mountain village school showed only 18 per cent positive. The high proportion of nonpulmonary tuberculosis is consistent with the status of tuberculization of the country.

Korns (2) in an analysis of 1248 Chinese tuberculous patients found 642 pulmonary and 606 nonpulmonary cases. This ratio is more nearly like that found in America, and is quite the reverse of the Syrian statistics. The author also states that there is an excessive amount of tuberculosis among the Chinese, and that they respond well to treatment when placed in the proper environment.

Outside of the lungs, the bones and joints, intestines and peritoneum, and lymph nodes have the largest numbers of cases (table 2). Males have more tuberculosis than females. There are also more male cases of bone and joint tuberculosis, while the females predominate in the intestinal and peritoneal and lymph-node groups. Of the bones and joints the spine is far ahead of any other member of this group: 76, or 24.8 per cent, as against 28, or 10.5 per cent, for the hip, the next highest (table 3). The inability of the bone to put up either a good cellular or humoral

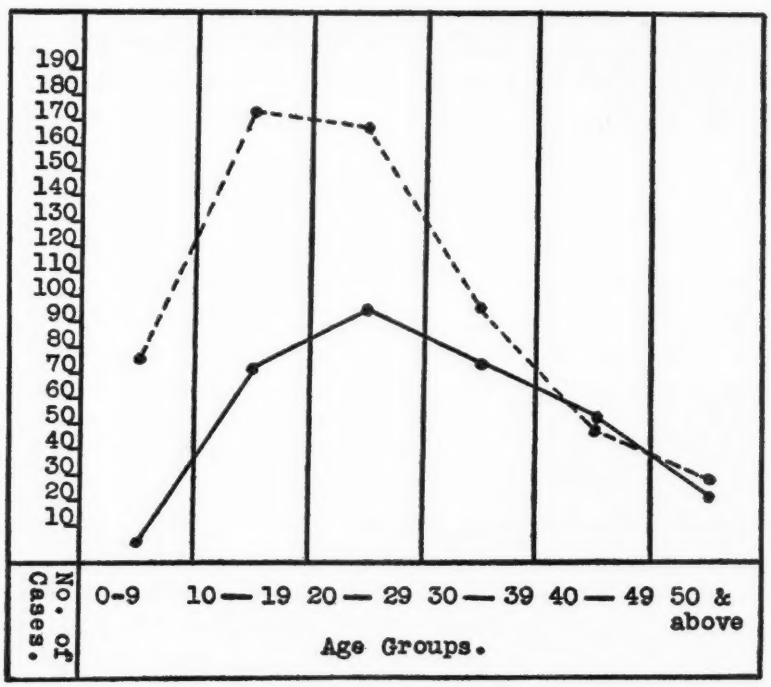

CHART 1. PULMONARY AND NONPULMONARY CASES BY AGE-GROUPS AMONG SYRIANS
———Nonpulmonary, ——— Pulmonary

defense probably accounts for the excess of tuberculosis in the bones and joints and especially in the spine.

The age of expectation for nonpulmonary tuberculosis is definitely within the 10–29-year group, whereas for pulmonary tuberculosis it extends from 10 to 39 years (chart 1). But, fewer people in general are likely to have pulmonary tuberculosis, although the bacillus enters through the lungs in the vast majority of cases. The reaction in the lungs among Syrians in both the exudative and productive types of tu-

TABLE 2

Distribution of tuberculosis by organs

ORGANS	SYRIANS		ARMENIANS		TOTAL
	Male	Female	Male	Female	
Lung	184	136	48	44	412
Intestine and peritoneum	63	85	15	16	179
Bones and joints	168	98	19	13	298
Lymph nodes	50	78	8	11	147
Meningitis	3	1	5	1	10
Skin	5	2	0	0	7
Tube	0	12	0	2	14
Testicle and epididymis	7	0	4	0	11
Kidney	2	5	2	1	10
Pleura	14	12	5	1	32
Brain	1	2	0	0	3
Miliary	6	5	1	1	13
Miscellaneous	6	6	2	0	14
Total	509	442	109	90	1,150

TABLE 3

Distribution of bone tuberculosis among Syrians

	MALE	FEMALE	TOTAL
Frontal	1	0	1
Maxilla	3	0	3
Ribs	22	3	25
Scapula	3	0	3
Sternum	4	1	5
Humerus	3	3	6
Elbow	7	2	9
Wrist	1	6	7
Metacarpal	1	1	2
Spine	46	30	76
Pelvis	1	7	8
Sacroiliac	3	3	6
Hip	12	16	28
Femur	8	5	13
Knee	16	10	26
Tibia	12	3	15
Fibula	1	0	1
Ankle	19	2	21
Tarsal	3	1	4
Metatarsal	2	4	6
Multiple	0	1	1
Total	168	98	266

berculosis is the same as that seen among Americans, both grossly and microscopically. The explanation of this excess of nonpulmonary over pulmonary tuberculosis among Syrians must be either that many more tubercle bacilli enter the blood-stream from the lungs or that the humoral reaction against the organisms is nil. The author feels that the latter explanation is the more logical in a nontuberculized race in which there is little or no hereditary immunity.

Molony (3) suggests that environment has something to do with immunity since the people in the rural Province of Saskatchewan, Canada, came from countries where the tuberculosis death-rate is from 80–300 per 100,000 and now strike an average of 40 per 100,000. Syria is not so favorably located as is the Province of Saskatchewan. The geographical location of a country undoubtedly influences the extent of various diseases. But hereditary racial immunity is equally as important. The American negroes were very susceptible to tuberculosis when first imported to the United States, and only now are they developing a moderate immunity. Syrians and Armenians now have a certain amount of immunity to tuberculosis, judging from the fact that they average 42 per cent tuberculin-positive (1). In generations to come they will undoubtedly develop more immunity as the percentage of positive tuberculin cases increases. Then pulmonary should predominate over nonpulmonary tuberculosis, and should yield to proper treatment.

SUMMARY

1. An analysis of 1150 cases of tuberculosis among Syrians and Armenians is made. These cases were admitted to the American University Hospital at Beirut from 1908 to 1929 inclusive.

2. Nonpulmonary tuberculosis is found to exceed pulmonary tuberculosis in a ratio of 738 to 412. More males have tuberculosis than do females.

3. Bone and joint tuberculosis predominates over all other types of nonpulmonary tuberculosis. In this group tuberculosis of the spine has the largest number of cases.

4. Racial immunity is briefly discussed.

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ATELECTASIS AS A FACTOR IN THE EVOLUTION OF CHRONIC FIBROID PULMONARY TUBERCULOSIS[1]

HERMAN HENNELL

Advanced pulmonary tuberculosis is, as a rule, bilateral. Even when the disease is only moderately advanced in one lung there is some involvement in the "better" lung. A group of cases has long been recognized with extensive unilateral pulmonary tuberculosis which seems to be an exception to this general clinical rule. These cases usually give a history of many years of chronic cough with profuse expectoration, and with but few or no episodes of severe tuberculous toxaemia. As a rule they have always maintained a fair degree of health. Some have remained in apparently excellent physical condition and have been able to carry on normally despite the extensive pulmonary involvement. Furthermore, though the sputum has always been abundant, tubercle bacilli are found with increasing difficulty and may eventually disappear.

These patients present an extensive involvement of one lung, with displacement of the mediastinum and hemidiaphragm toward the affected side and considerable thoracic deformity. The shadow in the involved hemithorax is usually uniformly dense, obscuring the lung almost completely, and in the left-sided cases the cardiac shadow can be made out with difficulty. In some instances areas of lesser density may be discovered, usually in the upper lobe, which are apparently due to bronchiectatic or, less commonly, to intrapulmonary cavities. Because of the unilaterality of the process and the great difficulty of finding tubercle bacilli, despite the abundance of the sputum, it is frequently difficult or impossible to distinguish these cases from those with chronic nontuberculous lung disease with extensive fibrosis.

One rarely has the opportunity to observe the clinical course of such cases from their incipiency, as most of them are first seen by the physician when the pathological process is fully developed. The condition has commonly been regarded as an unusual form of chronic fibroid pulmonary

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tuberculosis in which the fibrosing process kept pace with the extensive ulcerative process in the lung. The unilaterality, which is the striking feature of this form of pulmonary tuberculosis, has never been satisfactorily explained and was accepted as more or less of a freak and an exception to the rule.

FIG. 1. A case of chronic pulmonary tuberculosis with extensive unilateral fibrosis. Note the marked displacement of diaphragm and mediastinum toward the involved left side. Tubercle bacilli have long disappeared from the sputum and the clinical picture is that of pulmonary fibrosis and upper-lobe bronchiectasis.

Figure 1 illustrates the characteristic roentgen-ray findings of this condition. In this patient after many years of chronic pulmonary disease, the process has remained unilateral. Furthermore, as far as can be ascertained, the pathological process was fully developed when the patient first came under observation, and its extent has varied little, if

at all, during many years. The clinical course, extending over many years, showed relatively few episodes of what might be interpreted as tuberculous activity with signs and symptoms of severe tuberculous intoxication. This patient has always enjoyed a fair degree of health, and during the last ten or more years has remained in excellent health, quite symptom-free, excepting for the one or two episodes daily of spasmodic cough preceding the expectoration of a moderate amount of sputum. Tubercle bacilli have long disappeared from the sputum, and the condition can be regarded as one of upper-lobe bronchiectasis in a chronic fibroid lung. This case is typical of the group and the significant features can be summed up as follows:

1: The extensive pathological process was fully developed when the patient first came under medical supervision many years ago.

2: The process has changed but little during these years, and the uninvolved lung has remained free from disease.

3: The clinical course was not characterized by episodes of "activity" with severe tuberculous toxaemia.

4: The patient is in excellent general health after many years of chronic pulmonary disease of tuberculous origin.

5: Tubercle bacilli have disappeared from the sputum many years ago and clinically the present condition is one of fibrosis of the lung with bronchiectasis, which, because of its localization in the upper lobe, has natural and satisfactory drainage and causes few symptoms.

The following case which has been under my observation from the incipiency of a similar process will perhaps illustrate the probable mechanism involved:

This patient is a young adult who has always been in good health and apparently free from pulmonary symptoms until about one month before he became acutely ill. During that month he was working unusually hard and did not seem able to throw off the "cold" which he believed he had. He often felt tired and very warm during the afternoon, but ascribed this to the summer heat and hard work. His loss of weight and strength was similarly explained. On July 28, 1930, he felt very tired, and though he worked the first part of the day he felt too sick to continue. That afternoon he visited a physician's office and a film (figure 2A) was made during that visit. The roentgen-ray evidence confirmed the physical findings of a left upper-lobe and probably also right apical tuberculous lesion, and clinically active, as evidenced by moderately high fever, productive cough, and recent loss of weight and strength.

The patient was seen by me two days later, at which time the physical signs were apparently unchanged and the temperature was 103.2°.

During the next twenty-four hours the temperature rose to 104.2°, and the signs in the left upper lobe changed to those usually found during the early stage of an upper-lobe lobar pneumonia, namely, marked dulness, bronchial breathing and no râles.

During the following four days the temperature continued high and the exudative process with signs of consolidation rapidly involved the entire left

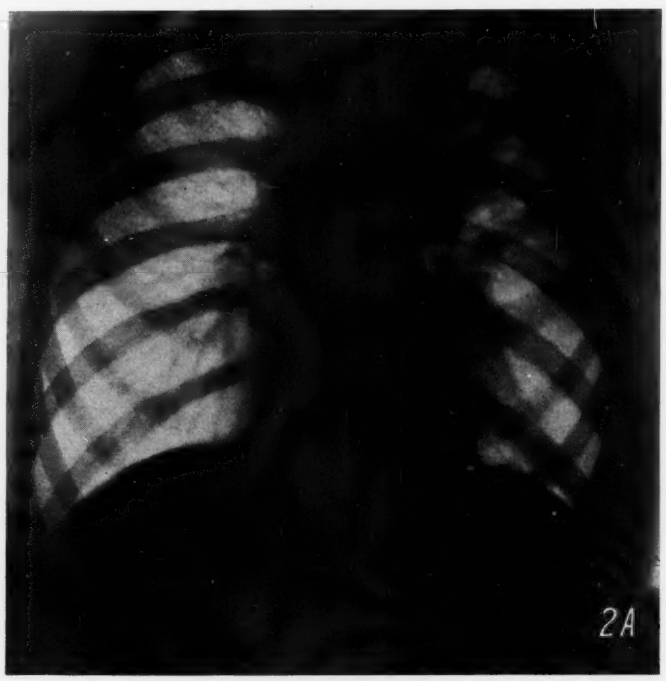

FIG. 2A. Roentgenogram, made on the day of onset of the acute illness. Note the chronic tuberculous process in the left upper lobe and right apical field. The mediastinal structures are in their normal central position.

lung. A film (figure 2B) was taken five days after that of figure 2A, and shows a uniformly dense shadow occupying the entire left hemithorax. The mediastinum is situated in its normal position. The presence of a large pleural effusion was suggested by the radiologist because of the uniformly dense shadow in the film. However, because the spread of the process from above downward occurred under my own observation, the diagnosis of an extensive exudative tuberculous pneumonia, lobar in type, seemed more probable. The physical signs were not conclusive one way or the other: resonance was markedly im-

paired throughout; no râles were heard; the breathing was bronchial in quality over the upper lobe and almost absent or very distant bronchial over the lower lobes; tactile fremitus was slightly decreased over most of the lung.

For nearly four weeks the clinical and pathological condition remained unchanged, the fever continued high, the cough and expectoration moderately severe, rapid loss of weight and strength proceeded, and the outlook seemed uncertain.

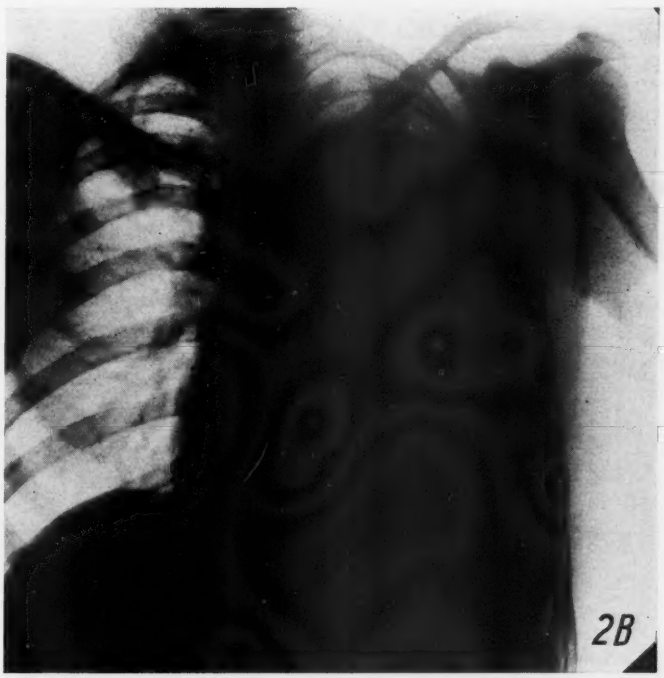

FIG. 2B. Roentgenogram (bedside), made five days later, shows a uniformly dense shadow occupying the entire left hemithorax. The mediastinum is still in its normal position. The exudative process was observed to spread rapidly from apex to base.

Rather unexpectedly the shifting of the mediastinum toward the involved left side was noted during the fifth week of illness. At about the same time the fever and the other symptoms began to show signs of improvement, which progressed at a more rapid rate during the two weeks following.

The film, figure 2C, was taken during the sixth week of illness, five weeks after figure 2B, and the most significant change observed in this film is the marked displacement of the mediastinal structures toward the affected left side. At the same time little or no clearing is evident in the film, and no discernible intrapulmonary fibrosis.

Rapid clinical improvement followed. The fever subsided, cough and expectoration decreased almost to the vanishing point, and tubercle bacilli disappeared from the sputum; weight and strength increased. At the same time fine dry râles, the type commonly heard over pulmonary lesions with fibrosis, appeared over the left lung below the fourth rib anteriorly and the seventh dorsal spine posteriorly, and only a few moist râles were heard over the upper lobe. The left lung showed no significant abnormal physical findings.

FIG. 2C. Roentgenogram (bedside), made five weeks later. Note the marked displacement of mediastinal structures toward the affected left side. There is little evidence of clearing or fibrosis.

The film, figure 2D, was made at the end of three and a half months of illness, when the patient was well enough to come to the office for examination. In this film moderate clearing of the process in the left lung is seen, but the shadow is still quite dense and the mediastinal structures are even further to the left.

COMMENT

It did not appear likely that pulmonary fibrosis of a degree sufficient to produce such marked mediastinal displacement, as shown in the film, figure 2C, could occur within five weeks in a lung which was the seat of an extensive rapidly developed exudative tuberculous pneumonia. Ordi-

FIG. 2D. Roentgenogram, made three and a half months after onset of the acute illness, shows moderate clearing of the process in the left lung, but the shadow is still quite dense and the mediastinal structures are even further to the left. Note the miliary or submiliary infiltration throughout the major portion of the right lung, a recent development.

narily an exudative tuberculous pneumonitis either clears up, partially or completely, in course of time, or goes on to caseation and rapid excavation. Fibrosis, if it appears at all, does so much later, after clearing has progressed a good way. In figure 2C, as was pointed out before, relatively little clearing is evident and intrapulmonary fibrosis cannot be discerned.

The probability of bronchial plugging with resultant atelectasis had to be considered as the more likely mechanism in the production of these marked pulmonary changes in so short a time. The absence of râles and the practically absent or very distant bronchial breathing, which were the significant physical findings elicited during these weeks, could most satisfactorily be explained on this hypothesis. A few weeks later, simultaneously with the appearance of the fine and coarse dry râles so characteristic of fibrosis, the roentgen-ray findings, as shown in figure 2D, were at least suggestive of progressive pulmonary fibrosis in a lung in which atelectasis had occurred and was apparently persisting.

The marked clinical improvement, which appeared almost abruptly in the sixth week of illness and progressed at an accelerated rate during the ensuing weeks, was particularly striking in view of the roentgen-ray changes which took place in the right lung since the film, figure 2C, was made. In figure 2D there is definite evidence of miliary or submiliary infiltration throughout the major portion of the right lung. This obviously was a recent development, and must have occurred as a result of an invasion by way of the blood-stream or lymph-stream in the right lung with the localization of the tubercles in the interstitial tissues and not in the alveoli. This mechanism of tuberculization of the right lung is suggested by the miliary nature of the lesion, and particularly by the absence of signs of bronchiolitis in the form of râles, as would have been the case had the process been bronchogenic. The apparent quiescence of the process in the right lung can best be explained by the localization of the tubercles in the interstitial tissues rather than in the alveoli, and, what is even more important, by the rapid subsidence of activity in the lesion in the left lung. The probable sequence of events can perhaps be summed up as follows: As an incident in the exudative pneumonitis in the left lung, bronchial plugging occurred and atelectasis of large portions of pulmonary tissue took place, which did not clear up as the exudative process began to subside. As a result of the pulmonary atelectasis, pulmonary fibrosis took place early and progressed rapidly. Consequent to the pulmonary rest brought about by the extensive atelectasis and subsequent fibrosis, the tuberculous toxaemia subsided rapidly. As a result of the early subsidence of the toxaemia, the recent process in the right lung has remained localized in the interstitial tissues and did not become complicated with a perifocal exudative pneumonitis of toxic origin.

There is nothing fantastic about this suggested mechanism. That atelectasis is an integral, if not an important element in the pathology

of nontuberculous pulmonary inflammation, is well established. In bronchopneumonia, for instance, the characteristic appearance of the involved lung is the result of areas of exudation, of atelectasis, and of emphysema scattered throughout the involved pulmonary tissue. In lobar pneumonia the size of the involved lung, as well as the nature of the physical findings, are determined by the extent to which atelectasis, resulting from bronchial plugging, is a factor. As is well known, the pneumonic lobe is usually larger, but occasionally it may be smaller than the expanded normal lobe. It is rare, but not too uncommon, for the physical and roentgen-ray findings in lobar pneumonia to show marked diminution in size of the involved lung, as indicated by the displacement of the heart and mediastinum toward the affected side, elevation of the corresponding leaf of the diaphragm, narrowing of the intercostal spaces and increased downward inclination of the ribs on the involved side. In such cases the usual physical findings of lobar pneumonia are absent or modified and the impression is strong that the unusual physical and roentgen-ray findings in these cases are due to plugging of the bronchus, leading to the collapse of the involved area during the early stages of the exudative process. That similar pathological processes may occur even more commonly in the evolution of pulmonary phthisis has recently been demonstrated (1)(3). In ordinary pneumonia the atelectasis usually clears up readily; and when, in the exceptional case, it fails to do so, extensive pulmonary fibrosis, with subsequent bronchiectasis or pulmonary suppuration, inevitably follows. When it occurs in a tuberculous process the tendency is for the atelectasis to persist, in whole or in part, probably because of the chronic character of the inflammatory process, with resulting cirrhosis of the lung and all its sequellae.

In this connection the behavior of tuberculous lung tissue under compression therapy is quite illuminating. As was pointed out in a previous study (2), the apparently "selective" action of pneumothorax (and this is equally true of phrenicectomy or thoracoplasty) to bring about the collapse or atelectasis of diseased areas wherever they may chance to be localized, whether in the upper lobe or lower, or any portion of either, is based upon the marked tendency of inflamed lung tissue to become and remain atelectatic when favorable conditions are created. The mechanism of this selective collapse or atelectasis has been described in detail elsewhere and need not be gone into at this time.

Once atelectasis has occurred in an inflamed area, whether as a result of gross bronchial occlusion or through one of the other mechanisms dis-

cussed in a previous study (3), fibrosis develops very rapidly. As was shown by ample necropsy material (4), the amount of fibrous tissue which forms in a collapsed tuberculous lung is greatly in excess of that in an uncompressed tuberculous lung. Sauerbruch's experience in this connection is very illuminating. He found at necropsy in one of his cases a marked tendency toward the encapsulation with young connective tissue of all tubercles and caseous nodules in a lung which was compressed by a thoracoplasty only three months before death. At the same time the uncompressed "better" lung showed extensive caseation, with cavity-formation, but without any tendency toward fibrous encapsulation. In this case the thoracoplasty was performed as a palliative measure because of repeated large haemorrhages from the cavities in the more diseased lung in spite of active disease in the other side. The striking feature of this case is that a far-advanced lesion in the compressed lung of a dying person was able to progress far toward arrest in a period of three months, while at the same time there was little or no evidence of healing by fibrosis in the uncollapsed lung. Whether this increased fibrosis is due to a stasis of lymph, rich in toxic metabolic products, or to chronic passive congestion, or to loss of pulmonary function, or to other causes is a debated issue. But there is no question as to the beneficial effects of fibrosis in limiting the spread of the disease and preventing toxic absorption. The reduction of tuberculous toxaemia not only releases the nervous system and all other organs from chronic poisoning, which is responsible for the constitutional symptoms, but also eliminates focal reaction in other infected areas, thus preventing their activation and spread.

In the case of the young man, whose history was detailed before and illustrated with figures 2A, 2B, 2C and 2D, the mechanism of the process was somewhat involved and difficult to elucidate. How definite and clean-cut the process can be, and how acute its onset, was shown in another case reported in detail elsewhere (3). By permission of the editor (*Archives of Internal Medicine*) figures 3A, 3B, and 3C are reproduced here. Figure 3A shows a small fibroid apical lesion in the left lung, with normal position of the trachea and mediastinum. Figure 3B was taken within one hour after the sudden onset of acute respiratory symptoms suggestive of an acute attack of asthma, to which the patient was subject, but which was not relieved by adrenalin as on previous occasions. This figure shows atelectasis of the major portion of the left upper lobe, with resulting displacement of the trachea and upper mediastinum to the

affected side. This atelectasis persisted. The film, figure 3C, was made nearly three years later, shortly after another attack of severe respiratory symptoms. The appearance is characteristic of massive atelectasis involving most of the remaining left lung. The details of the mechanism in this particular case were discussed in the original publication, and the object of the present reference is to emphasize how the end-result of an extensive unilateral involvement can be evolved acutely through the

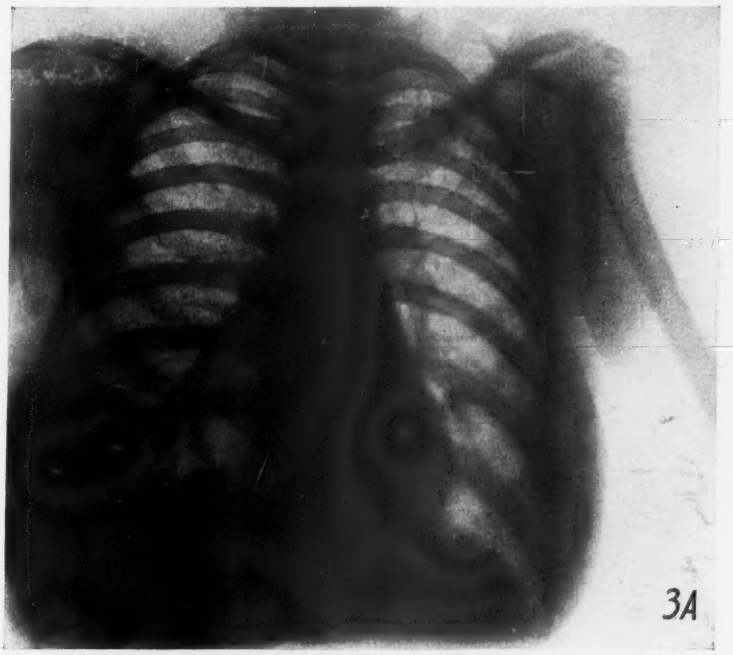

FIG. 3A. Roentgenogram, showing infiltration with fibrosis involving the upper portion of the left upper lobe. Note the normal position of the trachea and mediastinum.

mechanism of bronchial occlusion in a patient with a minimal initial tuberculous lesion.

When the pathological process is fully developed in these cases the roentgen-ray findings are so similar that films of different patients can be mistaken easily one for the other,—they have a family likeness. Unless their clinical course can be traced in all its details these cases are very confusing and are differently interpreted, depending upon the particular phase in which they come under observation. Furthermore, in course of time they differ very little, if at all, in their pathological process or their clinical course from the cases with extensive unilateral non-

tuberculous pulmonary fibrosis. Their chief symptoms are determined by the extent and localization of the bronchiectasis, and by the degree of cardiac and pulmonary embarrassment which inevitably and for obvious reasons result from marked cirrhosis of the lung.

In this connection, and as a therapeutic hint, it may be of interest to record the fact that in the last case the dyspnoea and palpitation, which were so distressing to the patient after the massive atelectasis of the left lower lobe occurred, were considerably relieved a few months later

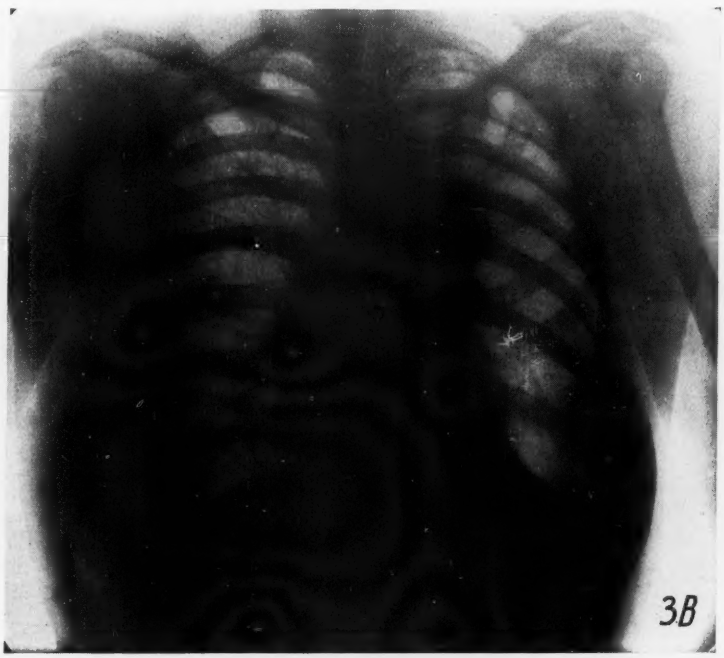

FIG. 3B. Roentgenogram, made one hour after the sudden onset of acute respiratory symptoms. Note the atelectasis of the left upper lobe with resulting marked displacement of the trachea to the left, as well as the less-marked displacement of the upper mediastinum.

when a pleural effusion developed on the affected side and caused the return of the mediastinal structures to their central position. This is shown in figure 3D. Because of such considerations, therapeutic pneumothorax or phrenicectomy, or even thoracoplasty may be occasionally employed with great benefit to the patient in the relief of the symptoms resulting from cardiac and mediastinal displacement. Occasionally the mobilization of the chest-wall by surgical procedures may release the pull of fibrous tissue on cavities, permitting their closure; and by a simi-

lar mechanism may prevent the formation of bronchiectasis. For, by allowing the chest-wall to approach the shrinking lung, the excessive pull of the fibrosing process is compensated and is not spent in either keeping cavities open or dilating the bronchi.

FIG. 3C. Roentgenogram, made nearly three years later, about two weeks after sudden onset of acute respiratory symptoms. The appearance is characteristic of massive atelectasis involving the major portion of the left lung. Bronchoscopic examination revealed stenosis of the bronchi of the left lung, probably due to marked peribronchial sclerosis with retained secretion of mucus.

On the other hand, the treatment of the bronchiectatic condition is not so simple. If it is localized in the upper lobe, where drainage may be satisfactory, the condition requires no special measures for relief. The lower-lobe bronchiectasis presents the usual difficult problem, but not different in this type of case from bronchiectasis in other patients.

When viewed in this light the mechanism of the pathological process in fibroid phthisis and of its clinical equivalent becomes apparent. It seems probable that atelectasis plays a more or less important rôle in the evolution of chronic fibroid phthisis of even limited extent. It is questionable if it precedes fibrosis in most instances. It undoubtedly occurs

FIG. 3D. Roentgenogram, made after the development of a pleural effusion, resulting in the return of the mediastinal structures to their normal central position and in the relief of the symptoms which had been caused by the abnormal displacement of the heart and mediastinum.

not infrequently, and by favoring rapid and extensive fibrosis retards or even prevents the development of ulcerative lesions. Cases, with a limited upper-lobe lesion and with marked deviation of the trachea and upper mediastinum toward the affected side, are probably illustrative of this mechanism. The atelectasis here is a conservative process and may

be responsible for the mild clinical course, as well as for the slow progress of the pathological process in this form of phthisis.

On the other hand, in the type of case with extensive unilateral pulmonary fibroid tuberculosis the mechanism of atelectasis is probably an important, if not the most important factor. The pathological process in these cases is essentially one of fibrosis in a comparatively mildly infected tuberculous lung in which large areas of atelectasis occurred. This will explain the rapid occurrence of the pathological process, the subsequent extensive fibrosis, the unilaterality of the tuberculous process and the relative mildness of its clinical course.

SUMMARY AND CONCLUSIONS

1. In the so called "advanced unilateral fibroid phthisis" massive atelectasis of large portions of pulmonary tissue, occasionally involving most of one lung, is probably the essential mechanism of the evolution of the clinical and pathological condition.

2. In this group of cases the tuberculous process in the lung may be minimal and its clinical significance may become relatively unimportant.

3. The marked pulmonary fibrosis, which rapidly develops after atelectasis occurs, eventually dominates the picture.

4. The tuberculous process may be submerged by the extensive fibrosis, and the bronchiectasis which follows in the wake of the pulmonary fibrosis may determine the clinical features and course in this group of cases.

5. It is probable that in the evolution of fibroid phthisis of lesser degree atelectasis involving smaller or larger areas of pulmonary tissue is an important factor. It is a conservative process and may be responsible for the mild clinical course as well as the slow progress of the pathological process after it is established.

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CHRONIC PULMONARY ATELECTASIS[1,2]

MILTON SILLS LLOYD

The subject of atelectasis has been treated by many authors and has been accurately and exhaustively described as an acute condition, in which bronchial obstruction is found secondary to a definitely indictable cause, either outside the bronchus, inside the bronchus, or within the bronchial wall.

The author desires to report his observations on 20 cases, in which no bronchial obstruction was found and in which the course was chronic and practically without symptoms. Symptoms present were in all cases attributable to some other morbid condition. To say "no bronchial obstruction" does not mean that there is no obstruction (there must be obstruction to produce atelectasis in an expanded lung), but it means that the obstruction is bronchiolar rather than bronchial and is therefore out of the range of vision of the bronchoscope. This type of atelectasis may be general or partial. Its onset is insidious and it advances by continuity and contiguity. It is therefore chronic and, as an entity, is clinically benign. This contrasts strongly with bronchial obstruction, in which the atelectasis is always massive, the size of the area involved depending only on the importance of the occluded bronchus. The latter type is therefore acute with a marked clinical symptomatology.

THE COUGH REFLEX AND ATELECTASIS

The possibility of a chronic atelectasis was half proved in the clinic of Chevalier Jackson, in Philadelphia, in experiments carried out by Lee, Tucker and Clerf on dogs (1). The secretion from a clinical human case of atelectasis was injected into the bronchi of the animals after they had been narcotized with ether. The area of lung supplied by the ramifica-

[1] The contents of this article are based upon a paper read before the Richmond County Medical Society by the author on May 8, 1929.

[2] Cases of children reported in this paper were prepared with the collaboration of Dr. E. Gordon Stoloff, from the Pediatrics Department of Dr. Bela Schick, at Sea View Hospital, New York City.

tions so occluded presented the clinical picture of atelectasis, without the presence of any other foreign body. On the other hand, secretions, placed high in the tracheobronchial tree, were coughed out. At the same time we know that nonviscid substances, such as saline solutions, gomenol solutions and liquid paraffine, may be injected in limited quantity into the small bronchi with impunity.

Recent work has shown that the parenchyma of the lung about the terminal bronchial divisions contains more musculature than has been hitherto believed and it is supposed, although not yet completely proved, that this muscle in the terminal bronchioles possesses peristaltic properties.

The mechanism for the protection of the lung, therefore, appears to be more involved and yet clearer than it was before. It may be compared to the removal of grain or sand by the endless-chain method. Men with shovels place small quantities of grain or sand on to the endless chain, which elevates or delivers it to empty trucks. The trucks then haul it away in large loads. In our analogy the men with shovels are the peristaltic bronchioles, the endless chain is the ciliated epithelium of the bronchi and trachea, and the trucks are the blasts of air in the larger bronchi and the trachea, resulting from the cough reflex. It is apparent that an interference with any one part of this mechanism would spoil the effectiveness of the whole. The most delicate part of this mechanism is the action of the ciliated epithelium, and it is consequently the most likely to be disturbed in function. To use a simile of Jackson, the movement of the cilia is like the waving of a field of grain before a gentle breeze. If this field be now suddenly covered with mud up to the level of the heads of grain there will be no more waving. This is exactly what happens when thick mucilaginous secretions collect in the lower bronchi. The cilia are then no longer able to move the secretions upward.

BRONCHOSCOPIC OBSERVATIONS

Through the bronchoscope a further mechanism may be observed, which, added to the above, completes the requirements for bronchiolar obturation.

A cough is preceded by a deep inspiration and the bronchi are widely dilated. Air rushes out during the cough, but does not attain any speed until the many small currents are combined in the upper large bronchi. The secretion adheres to the walls of the smaller bronchi and is not disturbed. At the end of the cough the bronchioles are collapsed and the

mucous layers come into contact and completely close the lumen. After the cough there is a short, quick inspiratory movement and the negative pressure in the lung parenchyma draws the plug further into the bronchiole, before it is penetrated by the pressure of the atmosphere from without.

Cough is, therefore, in such cases, not only useless but definitely harmful. In this way an inflammatory process in the lung may be continued indefinitely, because lobular atelectasis is the first step on the way to bronchopneumonia. We are also in a position to understand how secretions of the proper viscosity in the bronchioles cause atelectasis, and why pyogenic bacteria from the same starting point move outward and cause suppuration of the lung.

Another condition, which is observable through the bronchoscope and which may be an important factor, is the fragility or collapsibility of the bronchial walls. In two cases of our series this was a very notable feature, and in one case the operator believed the instrument to be in an inflamed oesophagus. It was only by exposing the carina and bifurcation that a differentiation could be made.

In this series all cases showed the presence in the bronchi of tenacious secretions, which in many instances would cling to the bottom of an inverted test-tube. Combine this type of secretion with a weak or easily collapsible bronchial wall and the production of atelectasis appears inevitable. When with this are associated a chronic bronchitis and a productive peribronchitis and interstitial pneumonitis, each newly involved area of atelectasis is "fixed" by a replacement fibrosis while a contiguous area is in process of becoming atelectatic.

X-RAY FINDINGS

The roentgenographic picture in cases of chronic atelectasis presents the same characteristics as in the acute condition, except that the area is sometimes smaller and not lobar in distribution. There is a diminution in the size of the affected lung, which shows increased opacity to the rays. All the surrounding structures, including the heart, the trachea, the diaphragm and even the chest-wall, are drawn into the hemithorax on the involved side. The bifurcation of the trachea is sometimes displaced more than an inch beyond the border of the sternum. Taking the midaxilla as the central point, the ribs have a fan-like appearance radiating outward. A lateral view reveals a typical contour of the diaphragmatic dome. The central point is higher and more peaked than

in the normal. The anterior half falls away sharply, is curved forward, and lies close to the chest-wall. The posterior half is nearly a straight line or may be slightly curved downward during forced inspiration.

On fluoroscopic examination the better lung is seen to be subjected to an abnormal degree of expansion during the inspiratory phase. The dome of the diaphragm is fixed. Laterally, the straightened posterior half of the diaphragm is seen to move backward and forward, rather than up and down. There may be a slight paradoxical movement upward of the diaphragmatic dome on the affected side at the end of inspiration. When the phrenic stimulus to the diaphragm begins to fall off, the balance of tension between the downward pull of the diaphragmatic muscle and the upward pull of the negative pressure in the atelectatic lung swings to the side of the lung, and the negative pressure, then at its maximum, "takes up the slack" of the relaxing diaphragm.

PHYSICAL SIGNS AND SYMPTOMS

In our series, there were 3 cases (nos. 837–28, 1681–29 and 2009–29) of pure (that is, uncomplicated) chronic atelectasis. In one case it was associated with lung abscess and in the remainder with pulmonary tuberculosis. One of the uncomplicated cases expectorated considerably at remote intervals. The other two had no clinical symptoms. On physical examination the involved hemithorax is comparatively small, and movement on that side is almost or altogether absent. The trachea is drawn markedly toward the affected side and, when the lesion is on the left, the apex beat of the heart is displaced upward and outward, being frequently found in the fourth interspace, about a half-inch outside the nipple line. The lung excursion is absent. Stethacoustical signs are very inconstant, but a careful search will reveal an area, generally posteriorly, where the signs of consolidation are present. To the alert clinician, this contrasts immediately with the good general condition of the patient. The lower lobe usually presents a mixture of fine and coarse râles and rhonchi, which are more noticeable during periods of expectoration and less so when sputum is absent.

ATELECTASIS AND COLLAPSE

By many writers and clinicians the terms *atelectasis* and *collapse*, as referred to the lung, are used as synonyms. As a matter of fact, they should be reserved and separated in our nomenclature for the description

of two conditions, which are entirely different. During his studies on this subject, the author has had occasion to bronchoscope four patients, who were receiving pneumothorax treatments. In one of them the collapse amounted to about 90 per cent. When the bronchoscope was inserted into the bronchus leading to the collapsed lung, this lung immediately resumed its function of respiration and the bronchi could be seen to dilate and contract, as in a normal lung. There was no sign of dyspnoea. In cases of atelectasis on the other hand, the insertion of the bronchoscope into the bronchus of the involved lung induced severe dyspnoea, and, in some patients, it was possible to examine the small bronchioles for a few seconds only, at a time. The term *collapse* should therefore be reserved for reference to pneumothorax only. An atelectatic lung is opaque to the X-ray; a collapsed lung is not. Atelectatic lung tissue contains no air; collapsed lung tissue contains some. An atelectatic lung cannot resume its physiological function for a period at least of hours. A collapsed lung can function physiologically, immediately on demand.

PROOFS OF ATELECTASIS

In two cases of our series, it was possible to demonstrate an increase of aeration following bronchoscopy. (Figures 1 to 9 and 11 and 12.) In all cases of this series, in which the pleura was not adherent, a high negative pressure, amounting to as much as minus 58 (true) cm. of water, was found within the thorax. In cases in which pneumothorax was established for therapeutic reasons, the collapsed lung showed an exceptional opacity to the X-rays (figures 14 and 15, 16 and 17 and the accompanying summary). The pleura did not show any evidence of thickening and no fluid was present. One case (no. 2182–29) presented the clinical picture of chronic atelectasis for about two years. Eventually, it was sent to Sea View Hospital. Tubercle bacilli were found in the sputum and the patient died in a few months. The autopsy report, provided by Dr. Vera Dolgopol for this paper, is as follows:

There is a dense fibrosis surrounding the bronchial distribution in the right middle and lower lobes. The fibrous tissue is old and collagenous. Several blood-vessels included in it show an extensive endarteritis. There is no fibrosis in the tuberculous areas proper, unless they are situated in the proximity of the fibrous tissue of the bronchial tree. The lesions in the tuberculous areas appear to be much more recent than the fibrosis. Dilatations of the bronchial tree are grossly visible throughout.

TABLE 1

Chronic pulmonary atelectasis: summary of cases

CASE NUMBER	SEX	AGE	ANTECEDENT DISEASE	ONSET OF PRESENT ILLNESS	LUNG AND AREA INVOLVED	SPUTUM		COMPLICATIONS	CLINICAL CONDITION	REMARKS
						Character	Bacteriology			
1047-28	F.	10	Bronchopneumonia	Cough, expectoration, October, 1927	Entire left lung	Tenacious	Pos. tub. bac.	Tuberculosis	Good	Collapsible bronchi, adherent pleurae
2320-29	F.	45	Cough, ten years	June, 1929, cough, weakness	Entire right lung	Mucoid	Pos. tub. bac.	Tuberculosis	Fair	Refused examination
1722-29	F.	15	"Influenza," August, 1928	Cough, fever, October, 1928	Left lower lobe	Tenacious	Pos. tub. bac.	Tuberculosis	Fair	Adherent pleurae
2565-29	M.	45	"Bronchitis," January, 1929	Cough, weakness, January, 1929	Entire right lung	Mucoid	Pos. tub. bac.	Tuberculosis	Good	Adherent pleurae, refused bronchoscopy
2087-29	F.	12	Pneumonia, spring, 1926	Cough, weakness, May, 1929	Entire left lung	Tenacious	Negative; g. p. inoc. neg.	Tuberculosis (X-ray)	Poor	Collapsible bronchi, haemorrhages
2510-29	M.	28	"Pneumonia," 9 years ago	Haemoptysis, May, 1929	Right lung	Mucoid	Pos. tub. bac.	Tuberculosis	Good	Refused examination
1736-29	F.	41	"Influenza," November, 1929	Sequel of influenza	Entire left lung	Tenacious	Pos. tub. bac.	Tuberculosis	Good	Refused examination
2172-29	F.	16	Pneumonia, July, 1929	Cough following pneumonia	Left lower lobe	Mucoid	Pos. tub. bac.	Tuberculosis	Good	Haemorrhages at onset
837-28	F.	14	Pneumonia, 5 years ago	*	Entire left lung	None			Excellent	Adherent pleurae
2009-29	F.	12	None	Bronchitis since January, 1927	Entire left lung	Tenacious	Strep. viridans		Good	Adherent pleurae
70-28	F.	24	None	Cough, December, 1927	Entire left lung	Mucoid	Pos. tub. bac.	Tuberculosis	Good	Intrapleural pressure, −24
1754-29	F.	14	Measles in infancy	Pain and fever, January, 1929	Left lower lobe	Mucoid	Pos. tub. bac.	Tuberculosis	Good	Intrapleural pressure, −44
2795-30	F.	36	None	Cough and fever, November, 1929	Entire left lung	Tenacious	Pos. tub. bac.	Tuberculosis	Poor	Adherent pleurae
2504-29	F.	11	None	Haemoptysis, 4 months ago	Left lung	None		Tuberculosis	Poor	Faeces pos. tub. bac.; Pleural pressure, −12
836-28	M.	41	Measles in childhood	Cough, April, 1928	Left upper lobe	Mucoid	Pos. tub. bac.	Tuberculosis	Fair	Intrapleural pressure, −58
2390-29	F.	15	None	Cough and fever, August, 1929	Left lung	Mucoid	Pos. tub. bac.	Tuberculosis	Poor	Intrapleural pressure, −32†
2582-29	F.	30	Bronchitis since childhood	Cough and fever, August, 1929	Entire left lung	Tenacious	Pos. tub. bac.	Tuberculosis	Fair	Intrapleural pressure, −32
2182-29	F.	4	Pneumonia, 2 years ago	Sequel of pneumonia	Right lower lobe	Thick	Streptococcus	Tuberculosis	Died (autopsy)	Old atelectasis, recent tuberculosis
815-28	M.	52	None	Cough, September, 1927	Left upper lobe	Tenacious	Staphylococcus	Lung abscess	Died	Recurrent atelectasis and aeration
1681-29	F.	7	Pneumonia, 6 months ago	Expectoration, January, 1929	Left lower lobe	Tenacious	Acid-fast bacillus		Good	G. p. inoc. neg.; collapsible bronchi; re-aeration after bronchoscopy; intrapleural pressure, −20

* This patient was admitted to King's County Hospital because of laryngeal symptoms sequel to diphtheria. The pulmonary condition was discovered on examination.

† All manometer readings given in true pressures. In this case the intrapleural pressure was so high that the liquid was drawn out of the manometer.

COURSE AND PROGNOSIS

Conclusions in respect to course and prognosis can, unfortunately, be based on only three cases in this series, since in these only is the condition unassociated with some other disease. Case no. 837–28 has been under institutional observation for a period of two years, without clinical symptoms. Case no. 2009–29 has been under observation for a period of one year without symptoms, and case no. 1681–29 for a similar period with only an occasional expectoration of greenish mucopus.

On account of the peculiar mechanical disturbance produced by the disease, in particular the tremendous outward pull on the lower part of the involved lung, one is bound to anticipate the yielding of the weaker parts and the dilatation of the blood-vessels and bronchi as a result.

In pursuance of this idea, lipiodol was injected into the left bronchus of the last two enumerated cases. Two important observations may be made from the resultant X-ray films (figures 28 and 29): first, the oil is not disseminated throughout the lung parenchyma, because of the replacement fibrosis, and, second, it shows a definite clumping, especially in the cardiophrenic and costophrenic angles, which is doubtless due to beginning bronchiectasis. Further observation after a lapse of another six months is required in these two cases.

TREATMENT

The indication obviously is to secure lung drainage. This can be partly accomplished by the bronchoscope, but it is not sufficient. The normal movements of the lung are necessary, and these are abolished as soon as atelectasis is established. The lung must be re-aerated. The author has attempted to accomplish this by the following means: (a) forcing the patient to breathe in the affected lung area, by placing the mouth of the bronchoscope over the corresponding bronchus; (b) directing oxygen under regulated pressure into the bronchus corresponding to the affected area; and (c) prescribing deep-breathing exercises with oxygen and carbon dioxide directed to the mouth under regulated pressure. It is too early to make any comments on the effectiveness of these methods.

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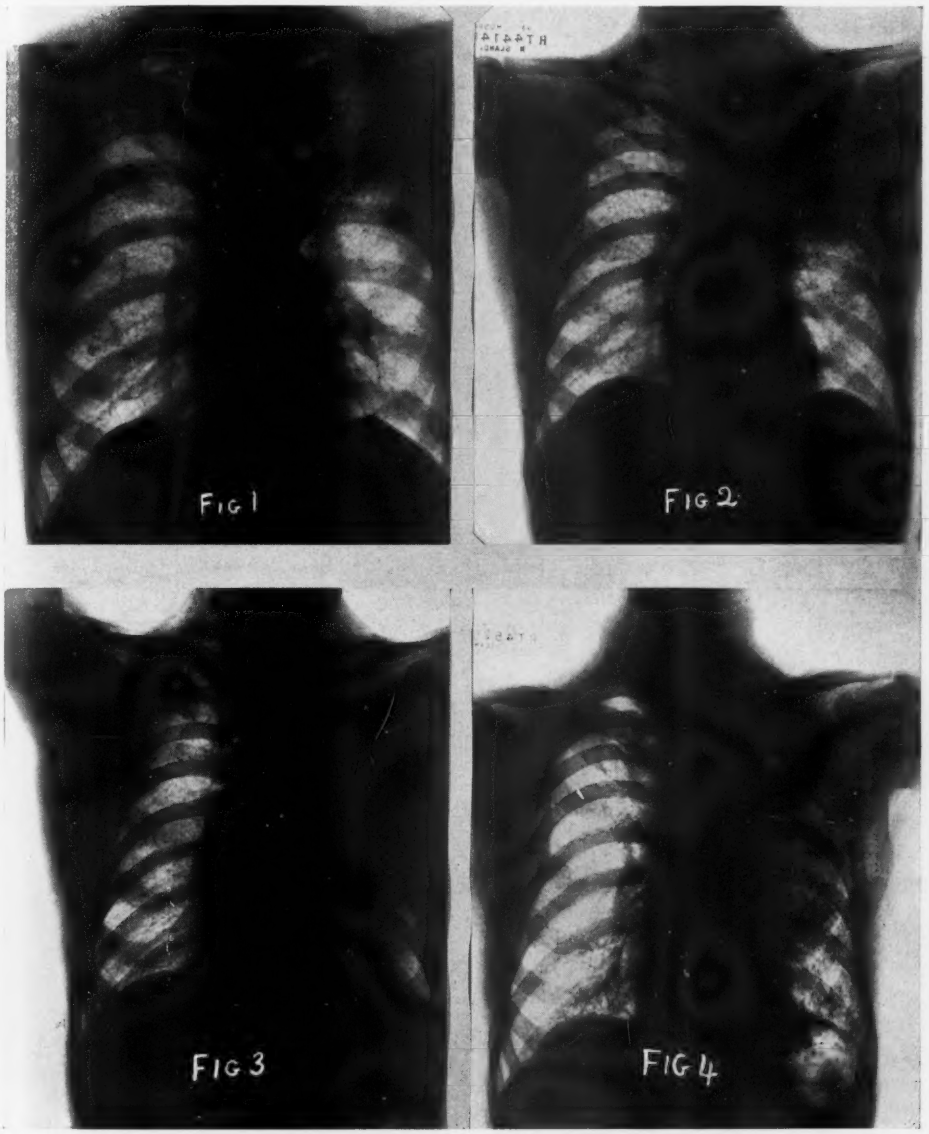

FIGURES 1 TO 10

Case no. 815–28. Pulmonary suppuration of unknown aetiology.

Fig. 1, taken November 30, 1927, shows an inflammatory lesion of the left apex, with a cavity at the 1st interspace.

Figs. 2 to 10, a series taken between July 26, 1928, and August 26, 1929, show a gradually increasing atelectasis, with intercurrent aeration, following bronchoscopic aspirations, in figs. 4, 6, 7 and 10.

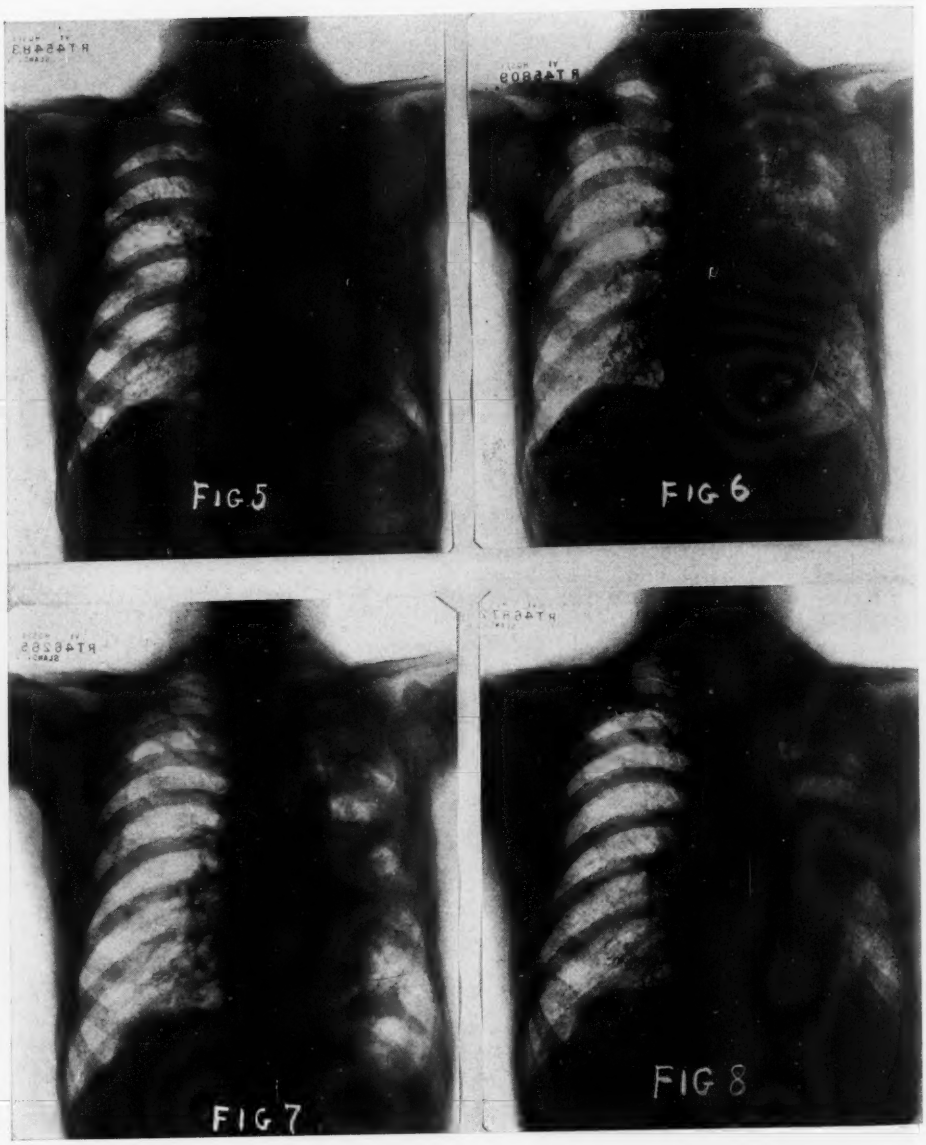
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FIG 7
FIG 8

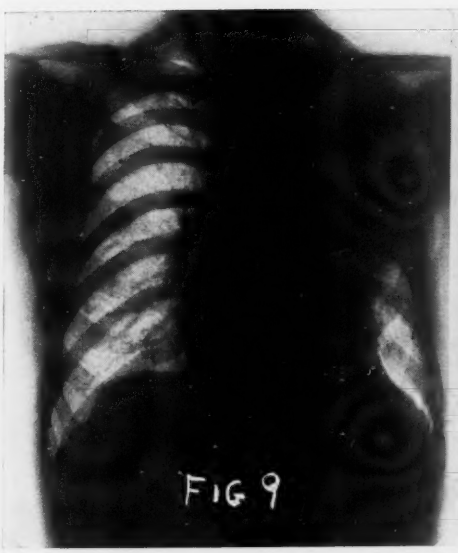


FIG 9

FIG 10

FIGURES 11 TO 15

Case no. 1681–29. Chronic pulmonary atelectasis in a girl seven years old.

Fig. 12 shows aeration after bronchoscopy, as compared with fig. 11.

Fig. 13, six months later, shows marked improvement by X-ray.

Fig. 14 shows return of almost complete atelectasis, associated with a winter cold and three weeks after an injection of lipiodol.

Fig. 15 shows re-aeration six weeks later. (Figs. 11, 12 and 15 are reversed in reproduction.)

Fig 11

Fig 12

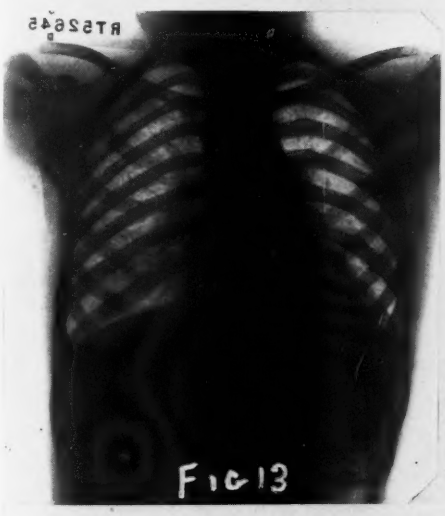
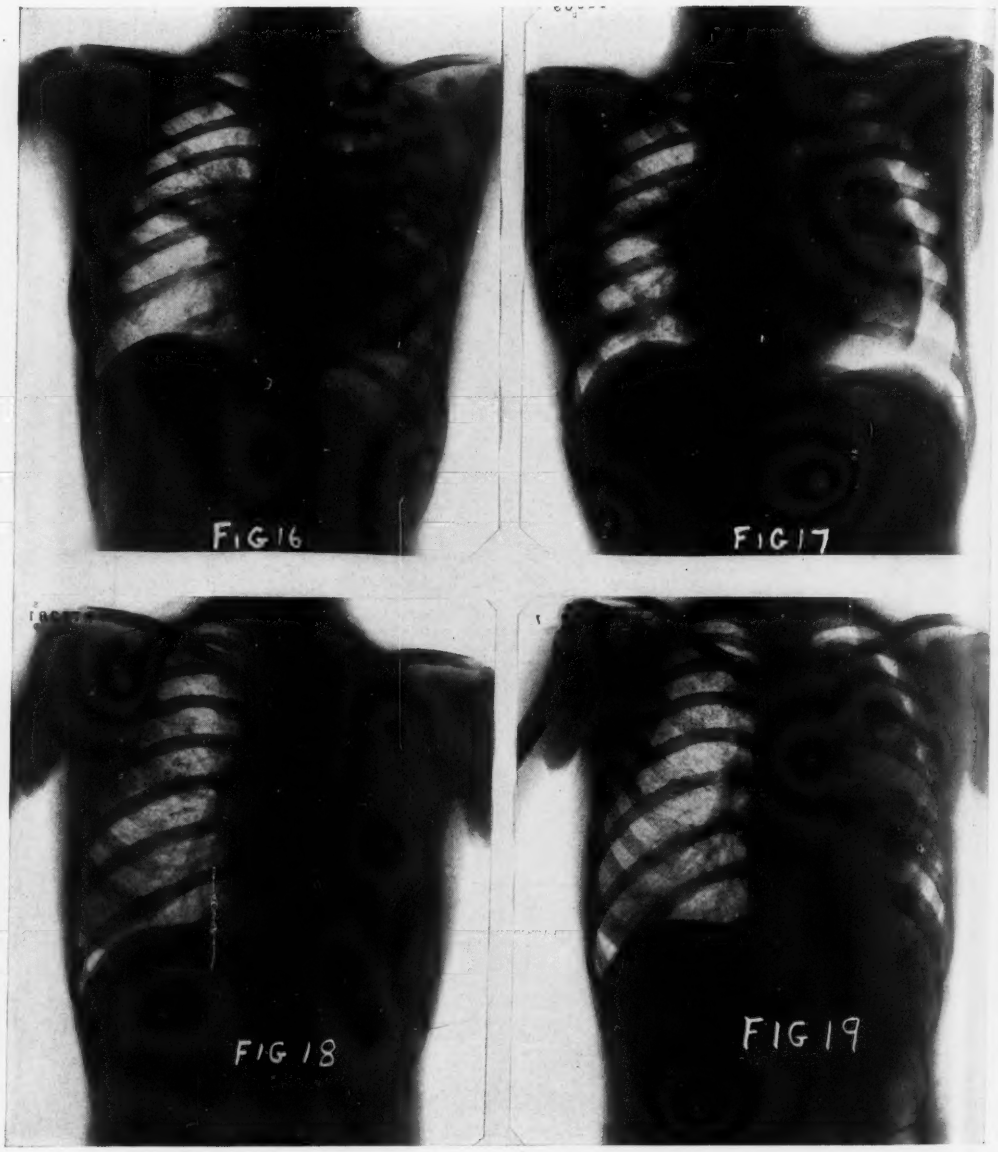


Fig 13

Fig 14

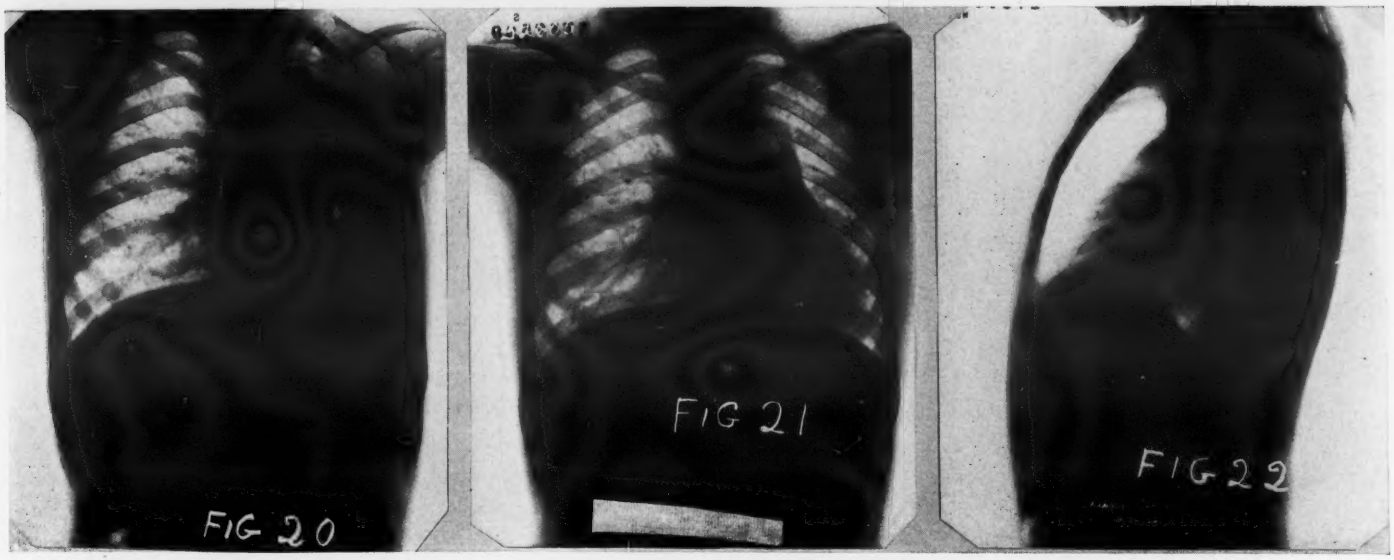
Fig 15.



FIGURES 16 TO 19

Cases no. 2390–29 and 2582–29. Atelectasis associated with chronic pulmonary tuberculosis.

Figs. 16 and 17, and 18 and 19 show these patients before and after artificial pneumothorax. (For intrapleural pressures see summary, table 1.)

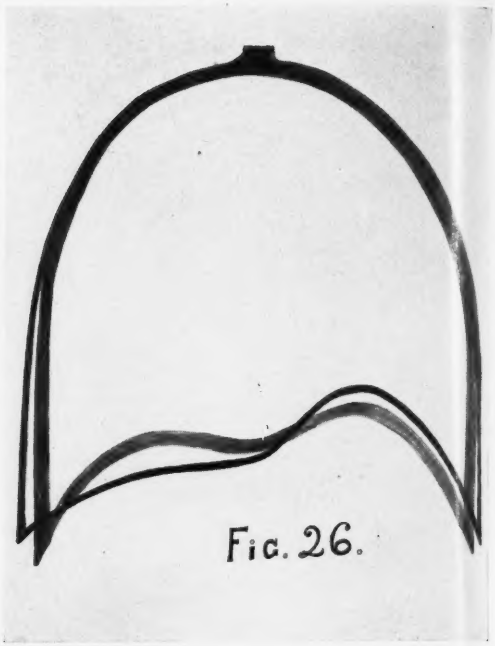


FIGURES 20 TO 22

Case no. 2009–29. Chronic pulmonary atelectasis in a girl twelve years old.

Fig. 21 shows remarkable clearing of the lung field as compared with fig. 20. (As in case no. 1681–29 the clinical condition remained good without associated changes.)

Fig. 22 shows the characteristic lateral view of the diaphragm.



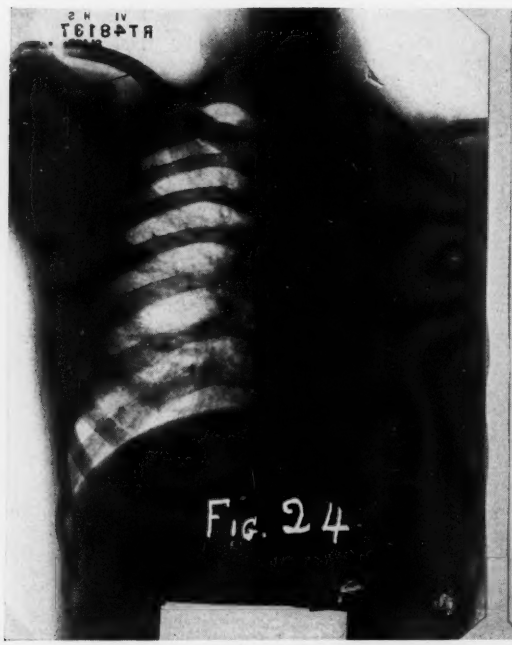


Fig. 23. Shows the characteristic lateral view of the diaphragm.

Figs. 24 and 25. Case no. 837–28. Show anteroposterior and lateral views of chronic pulmonary atelectasis, in a girl fourteen years old, unchanged for two years without clinical symptoms. (The arrow indicates the dome of the diaphragm.)

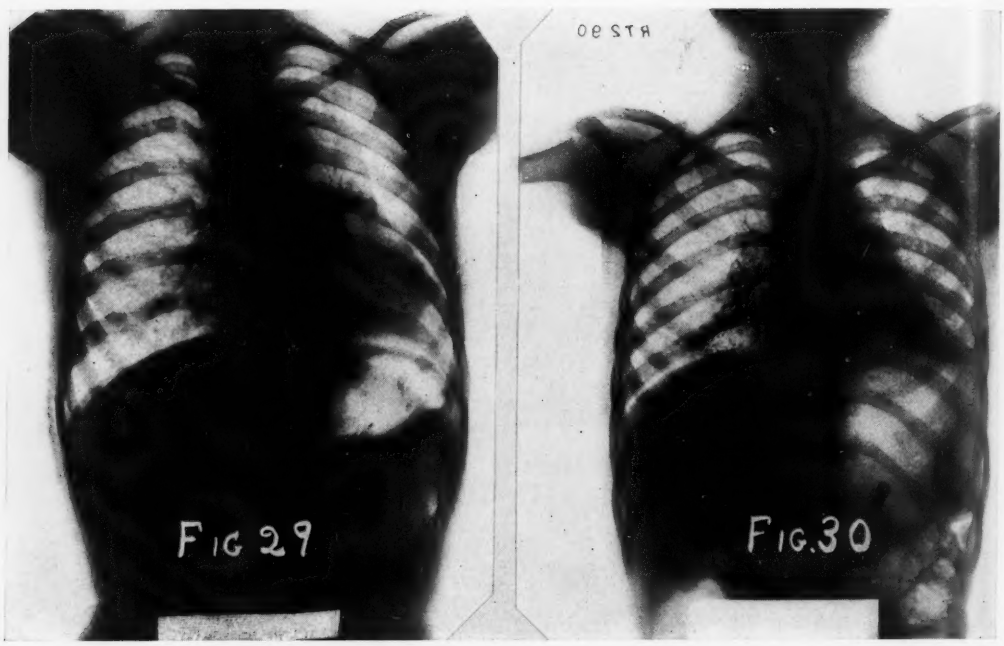
Fig. 26. Shows schematically the paradoxical movement of the diaphragm as seen in fluoroscopy. The thick line represents the diaphragm in expiration, the thin line in forced inspiration.

FIGURES 27 AND 28

Case no. 2182–29. Chronic pulmonary atelectasis, complicated by chronic pulmonary tuberculosis.

Figs. 27 and 28 are films taken one month apart. The inverted "V" indicates the displaced bifurcation.

FIG. 28a. Shows long-standing collagenous fibrosis, with advanced endarteritis, together with recent tubercles in a section taken from the right middle lobe at autopsy. (See text for autopsy findings.)



FIGURES 29 AND 30

Cases no. 2009–29 and 1681–29.

Figs. 29 and 30 show lipiodol injections of the lungs of two children, after two years and one year, respectively, of chronic pulmonary atelectasis. There is a poor distribution of the oil throughout the pulmonary parenchyma, probably because of fibrosis, and a clumping of the oil in the costophrenic and cardiophrenic angles, probably due to early bronchiectasis. (Most of the oil on the right side of the midline, below the diaphragm in fig. 30, is outside the body.)

ATELECTASIS IN PULMONARY TUBERCULOSIS[1]

EPHRAIM KOROL[2]

Atelectasis is of frequent occurrence in pulmonary tuberculosis, and is the cause of many physical and X-ray signs that are encountered in this disease and which are being attributed to the tuberculous lesions.

PATHOLOGICAL CONSIDERATIONS

As shown by Husten (1) in his studies of serial sections of tuberculous lesions, the tubercle bacillus finds lodgment in the terminal bronchioles where the ciliated epithelium is not present; here tubercles develop. The air-cells distal to the terminal bronchioles collapse and eventually become indurated.

Large bronchi are also frequently invaded and occluded by the tuberculous process. In the pneumonic type of pulmonary tuberculosis, areas of atelectasis are frequently seen at some distance from the tuberculous process. Upon careful sectioning of the lung tissues the supplying bronchi can be shown to be occluded by caseous masses. At times it is difficult to show the collapsed alveoli histologically, because during the preparation of the sections the alveoli may take up air or water and dilate (2) (3).

In chronic fibroid tuberculosis, Loeschke (4) finds extensive atelectasis to be of common occurrence. By means of serial sections this worker has been able to show the occlusion of a bronchus by scar-tissue or caseous material associated with every case of atelectasis. Other authors have made different observations and believe that the bronchial occlusion is not the only cause of atelectasis in tuberculosis.

Delafield and Prudden (5) also describe atelectasis in tuberculosis. In the illustrations appearing in their text-book, tuberculous invasion of the bronchi is conspicuous.

Ziegler (6) states that tuberculous inflammation of bronchi is a usual

[1] Published with the permission of the Medical Director of the U. S. Veterans Bureau, who assumes no responsibility for the opinions expressed by the writer.

[2] U. S. Veterans Bureau, Omaha, Nebraska.

accompaniment of pulmonary tuberculosis. His text-book contains a histological illustration showing two bronchi occluded by caseous material. Pagel and Henke (7) in their recent work on tuberculosis also dwell on the subject of atelectasis and show illustrations of caseous bronchitis with atelectasis of the supplied lobules.

Large tuberculous lymph nodes, by pressure on the trachea or on bronchi, may cause not only patches of atelectasis, but even massive atelectasis. We observed complete collapse of one lung produced in this manner (see case 1). Stoloff (8), also Lerche (9) and Simon and Redeker (10), have reported cases of atelectasis caused by pressure of tuberculous lymph nodes on bronchi.

Apart from bronchial occlusion there are other factors which favor the development of atelectasis in tuberculosis. In tuberculous lesions the air-exchange is poor, as was first shown by Kreutzfuchs (11); particularly so in cavities where the pressure may be greater than atmospheric (12). Some cavities are shut off from the atmosphere or communicate with the trachea only during paroxysms of coughing. Lobules supplied by bronchi intercepted by such cavities are likely to be collapsed, even though the bronchi be patulous or dilated. The blood-vessels about the tuberculous lesions are frequently obliterated by compression, endarteritis or thrombosis; this may lead to atelectasis of the lobules supplied by such vessels.

The clinical course of pulmonary tuberculosis and the very methods of treatment rather predispose to the development of atelectasis. The patient is confined to bed for months; he is advised to breathe with little effort and to cough as little as possible. He is frequently forced to recline in a certain posture for long periods of time, and may be prevented from coughing by pain or by fear of haemoptysis. These factors are conducive to the formation of massive atelectasis.

Judging from case reports in the literature, massive atelectasis is common in tuberculosis. We encountered in our hospital experience five cases of massive atelectasis, which developed without any relationship to operation or trauma; four of these cases occurred in pulmonary tuberculosis.

THE X-RAY SIGNS OF ATELECTASIS OCCURRING IN PULMONARY TUBERCULOSIS

The small lung, with elevated diaphragm and displacement of the mediastinum to the affected side, is a characteristic anatomical finding in pulmonary tuberculosis. It is generally supposed that the diminution

in size of the lung is due to fibrosis and that the visceral displacement is caused by contracting fibrous adhesions. However, these changes are frequently observed very early in the process, before adhesions of any extent could form; they also occur in the pneumonic and miliary types of the disease in which adhesions and fibrosis are not conspicuous occurrences.

Bushnell (13) finds displacement of the heart a very early sign and a delicate index of the existence of disease of the lung.

Norris (14) finds a decrease in the entire hemithorax, revealed by mensuration, in unilateral incipient tuberculosis.

Artificial pneumothorax is induced without difficulty in many of these cases (see figures 3a and b). During the first induction it is generally observed that the intrapleural pressure is lower than the accepted average normal. After enough air is introduced to raise the pressure to the normal level, the diaphragm and mediastinum shift to the normal position.

In some cases of pneumonic tuberculosis, the patient when first examined may show disease of one lung, with displacement of the heart to this side. During the course of the disease, as the other lung becomes involved, the heart may be seen to have returned to the normal position (case 2).

During fluoroscopic as well as physical examination of many of these cases, the heart may be seen to change position readily with changes in the patient's posture (case 3).

In cases of favorable progress, at the beginning of treatment the affected lung appears small and the heart displaced. As the tuberculous process recedes the lung may be found larger and the heart in the normal position (case 4).

During fluoroscopic examination of cases with predominantly unilateral tuberculosis, the mediastinum shows the pendulum movement of atelectasis, that is, it moves toward the affected side during deep inspiration and returns to the normal side during forced expiration (see cases 5 and 6).

The above observations plainly show that the contracted lung of tuberculosis and the concomitant visceral displacements are not always due to adhesions and cicatrization, but are more often a manifestation of airlessness of the affected lung, with the altered pressure relations.

PHYSICAL SIGNS OF ATELECTASIS ACCOMPANYING TUBERCULOSIS

In incipient cases inspection shows contraction of the affected side; this is best determined by mensuration. There is restricted mobility of this side.

Percussion gives signs of contraction not only of the involved apex but of the entire lung, the diaphragm being elevated and making small excursions. As early as 1897 Williams (15) emphasized the impaired movement of the diaphragm and its high position in the incipient stage of tuberculosis.

The earliest findings by auscultation are enfeeblement or total disappearance of the vesicular murmur and the gradual establishment of the bronchial murmur. Norris (16) finds feeble breath-sounds *throughout* the involved side. Fishberg (17) emphasizes, as the most common change, the feeble or absent vesicular murmur and the presence of the bronchial sound over the early tuberculous lesions. Fishberg recognizes atelectasis as the cause of the changed breath-sounds.

In more advanced lesions all of the physical signs become more pronounced; râles appear, and the mediastinal displacement comes into evidence.

That the typical "latent" râles of tuberculosis are due to atelectasis rather than to any specific tuberculous change in the lung tissue is now generally accepted as a fact. The râles are due to the opening and closing of the collapsed air-passages as a result of forced breathing. During cough (forced expiration) air is blown into these passages, separating their walls temporarily; during the succeeding inspiration the air-passages become devoid of air and they collapse again. This inflation of tuberculous areas during forced expiration and their collapse with inspiration (paradoxical breathing) may be observed under the fluoroscopic screen and can be shown on properly taken films (see figures 6 and 7).

After the tuberculous process becomes arrested, the atelectatic areas show the presence of an increased amount of fibrous tissue and the alveoli are then permanently collapsed and râles can no longer be elicited.

Without recognizing atelectasis as the essential factor in the production of the physical signs enumerated, it becomes difficult to explain their mechanism. Why should an incipient lesion, of a few weeks' duration, limited to a portion of an apex, produce contraction of the entire lung, limited mobility of the entire side of the chest, feeble breathing throughout the involved lung, displacement of the heart and diaphragm, and disappearance of the vesicular murmur over the site of the lesion?

If the specific tuberculous infiltration were the important factor in the production of the physical signs, we would expect, in lesions of short duration, rather an increase in the lung volume, and certainly no retraction over the lesion or at distant points, and no constant râles which persist indefinitely and which can be provoked very easily each time the patient coughs.

THE MECHANISM OF THE USUAL PHYSICAL AND X-RAY SIGNS IN TUBERCULOSIS

The normal negative tension in the pleural cavity is due to the relative disproportion in size between the chest and the lungs. In the adult the lungs seldom fill the pleural cavities to capacity except in cases of extreme emphysema. In the newborn the lungs completely fill the chest; the intrapleural pressure during this period of development is atmospheric. In later life negative intrapleural pressure develops as the chest grows more rapidly than the lungs and heart (18).

With the decrease of the lung volume in atelectasis or cicatrization of the lung tissue, there is an increase in the negative intrapleural pressure on the affected side. The pressure on the opposite side being relatively increased, there follows a displacement of the mediastinum to the affected side. The diaphragm on the affected side is elevated by the intra-abdominal pressure which amounts to one atmosphere. The prevailing atmospheric pressure on the outside of the chest causes the crowding of the ribs, the deviation of the sternum and the curvature of the spinal column, all of which are frequently found in cases of atelectasis. These abnormalities are more pronounced during inspiration, because the intrapleural pressure is further lowered during this phase of respiration: the chest increases in size while the collapsed lung cannot inflate to fill the created space. During forced expiration the conditions are reversed: the mediastinum returns to its normal position or may be displaced to the opposite side. The increased intrathoracic pressure during expiration is spent, not in deflating the lungs as it normally would, but in displacing the mediastinum. Abnormally low intrapleural pressure has repeatedly been demonstrated by means of the manometer needle in cases of massive and other forms of atelectasis (19) (20).

As the absorption of air from the tissues is a rapid process, the visceral displacement is an early sign in tuberculosis, pneumonia, and in other diseases in which atelectasis occurs. The mediastinum is displaced to the affected side by the higher pressure on the normal side and the diaphragm is elevated by the relatively high abdominal pressure. The

chest-wall of the affected side as the result of a low intrapleural pressure is compressed by the atmospheric pressure of the outside. This explains the retraction of the chest-wall in early pulmonary tuberculosis.

Why the limited mobility and expansion of the affected side? Why the limited action of the intercostal muscles and of the diaphragm in incipient tuberculosis with early lesions? The text-books are not very clear on this subject.

Normally the atmospheric pressure inflates the lungs as the chest cavity is enlarged by the efforts of the inspiratory muscles. The atmospheric pressure thus assists the muscles of respiration. During expiration, as the intercostal muscles and the diaphragm relax, the abdominal pressure, which is that of one atmosphere or more, and the descent of the ribs cause the chest cavity to collapse as the air escapes from the air-passages. If considerable portions of the lungs are airless and removed from the influence of the atmospheric pressure, the respiratory muscles are hampered in their action, being called upon to enlarge the chest without the assistance of atmospheric pressure; they also have to overcome an increased intrapleural tension. Under these circumstances, the natural effect of unilateral tuberculous disease is limited chest movement on the diseased side, as well as limited excursion of the diaphragm (decreased complemental space).

Normally the contour of the diaphragm and the position of the liver are determined by the interplay of pressure forces in the chest and in the abdomen. It has been shown that the ligamentous attachments of the liver are not strong enough to support this organ, but that it is the suction effect on the diaphragmatic surface of the liver which holds it in position (21). In cases in which there is an increase of the intrapleural pressure, as in emphysema, the liver descends; conversely, when the intrapleural pressure falls, as in atelectasis, the liver will rise upward into the chest. The latter phenomenon explains the high position of the diaphragm in the cases of pulmonary tuberculosis.

In atelectasis the intrapleural pressure is greatly diminished during inspiration, as the chest increases in capacity, while the collapsed lung cannot inflate. During deep inspiration, therefore, the mediastinum is further displaced toward the affected side. During expiration the pressure conditions on the two sides are reversed. On the normal side the pressure is relieved by the escape of air from the lung; on the diseased side the pressure is relatively high during expiration so that a shifting of the mediastinum toward the normal side occurs. This explains the pendulum movement of the heart in tuberculosis.

Case Reports

Case 1: Diagnosis: Tuberculosis of mediastinal lymph nodes, with compression of left bronchus and atelectasis of left lung. First examined in August, 1928. *Complaint:* Gradually increasing shortness of breath, of ten years' duration. Cough with profuse expectoration. Loss of weight and strength. *Physical Signs:* The chest is markedly contracted at the left base, with expansion greatly restricted on this side. The apex impulse is in the fourth interspace outside

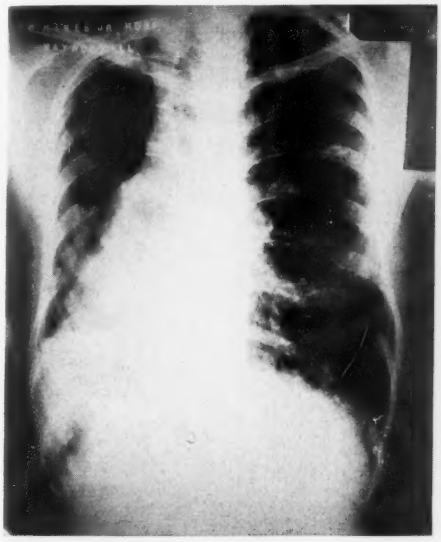


FIG. 1a

FIG. 1b

FIG. 1a. Case 1. Atelectasis of left lower lobe caused by pressure of tuberculous lymph nodes on lower-lobe bronchus. The left lung is very small. All the interspaces are narrow and the lower ribs are drooping on this side. Marked deviation of the heart and trachea to the left side and elevation of the diaphragm on this side.

FIG. 1b. Case 1. Lateral film of the same case, taken to show the enlarged calcified lymph nodes in the left hilum.

of left nipple line. No resonance on percussion over the base of the lung posteriorly and no breath-sounds. Coarse moist râles, during inspiration following cough, are noted over this area. Marked clubbing of the fingers. Eight ounces purulent sputum, which settles out in three layers in 24 hours; temperature normal. The fluoroscopic examination showed the left lung to be very small and relatively airless, and marked displacement of the heart and trachea to the left and elevation of the diaphragm on this side were noted. Large masses of lymph nodes were observed in the posterior mediastinum and in

both hila; they were particularly large on the left side where they extended to the tracheal bifurcation. Most of these nodes contained calcareous material. The heart shadow showed a prominence to the base on the left side, due either to an enlargement of the ascending aorta or to the pulmonary artery (the latter more likely). The blood tests were negative for syphilis and the blood examinations were normal. The diagnosis was in doubt for a long time, as the fluoroscopic observation of the calcified lymph nodes was delayed. Several attempts at locating fluid in left pleural cavity were unsuccessful. Syphilis of the lung was suspected and the patient was given intensive antisyphilitic treatment without any effect on the lung condition. Hodgkin's

FIG. 1c. Case 1. Fifteen months after fig. 1a. Complete collapse of left lung. Note the collapse of the chest-wall. The right lung is emphysematous. It has invaded the left hemithorax to an unusual extent. The honeycombed appearance in the region of the left upper lobe is due to saccular bronchiectasis.

disease and malignant tumor were ruled out by the long duration and the course of the disease. The patient presented himself for reëxamination in November, 1929. There was further contraction of the left side of the chest with further displacement of the heart. There were no breath-sounds over the lower lobe on the left side; over the region of the upper lobe bronchial breathing was heard. Fluoroscopically, the left lung was seen to be completely collapsed and there was extreme displacement of the viscera to this side. The right lung invaded the left hemithorax over a large area anteriorly, resembling pleural hernia seen in cases of pneumothorax under high pressure. (Figure 1a, b & c.)

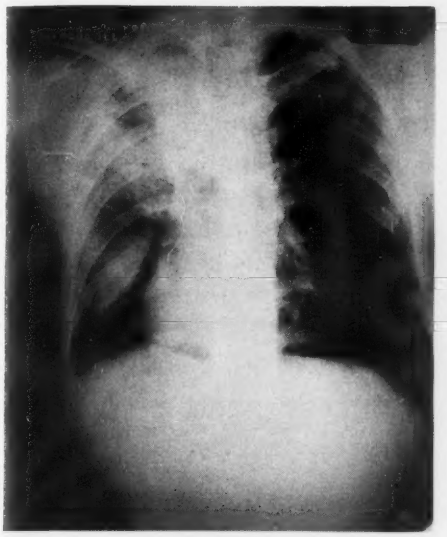


FIG. 2a

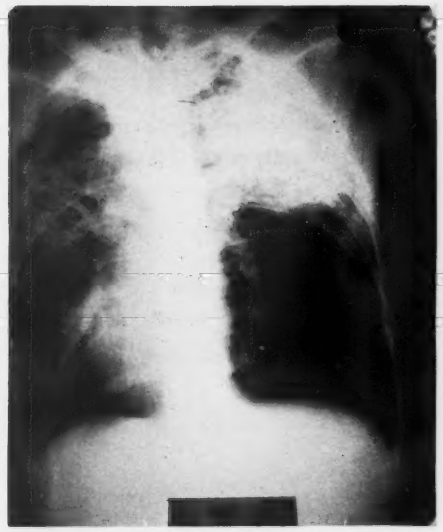


FIG. 2b

FIG. 2a. Case 2. October 16, 1929. Pneumonic tuberculosis of left upper lobe of four weeks' duration. The left side is contracted and the ribs are slanting. The heart and trachea are deviated to the left, the diaphragm is elevated on this side, and its costal sulcus is shallow.

FIG. 2b. Case 2. November 27, 1929. The tuberculous process has invaded the right lung. The heart and trachea are in the normal position; the two leaves of the diaphragm are in relatively normal position.

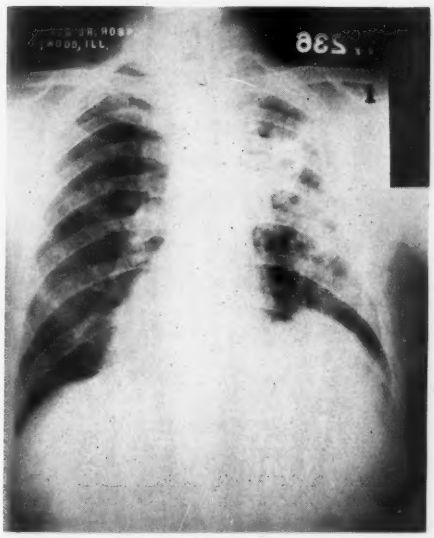


FIG. 3a

FIG. 3b

FIG. 3a. Tuberculosis of right lung. The right hemithorax and lung are contracted; the heart and trachea are displaced to the right and the diaphragm is elevated on this side.

FIG. 3b. Artificial pneumothorax induced without difficulty. The right hemithorax is normal in size. The viscera are in normal position.

Case 2: First examination October 16, 1929. *Complaint*: Weakness and loss of weight during the past four weeks; fever and night-sweats. Physical and X-ray findings were those of an extensive tuberculous pneumonia involving the left upper lobe. The heart is displaced to the left side. Sputum positive for tubercle bacilli. Reëxamination November 27, 1929: The lesion in the left lung is unchanged. There is a new large area of pneumonic consolidation involving the right upper lobe. The heart has returned to the normal position. (Figure 2a & b.)

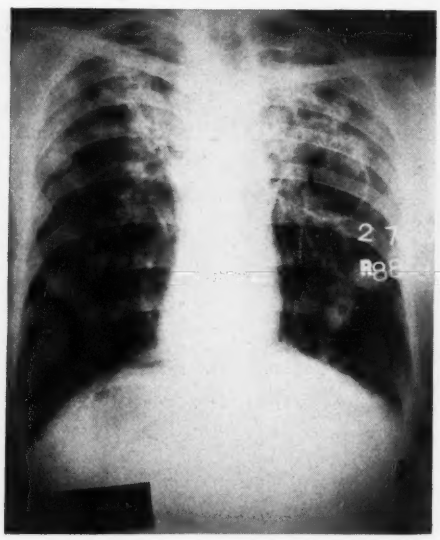


FIG. 4a

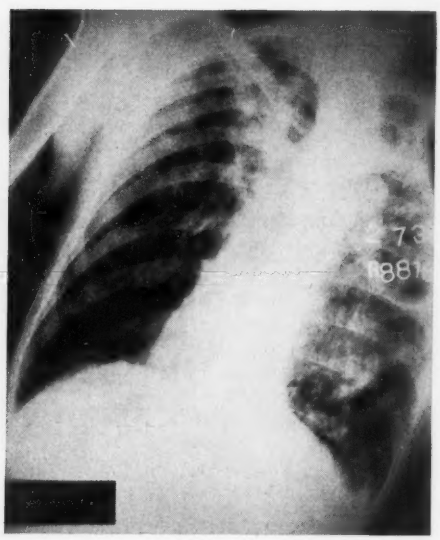


FIG. 4b

FIG. 4a. Case 3. Extensive tuberculosis with large cavity in right lung. Marked displacement of the heart to the right.

FIG. 4b. Case 3. Same case, taken with patient leaning over. The heart has moved over to the left side. It will be noted that in this position the diaphragm has ascended on the lower side; this lung is smaller and the ribs are slanting. On the upper side the ribs are horizontal, and the lung has enlarged particularly in the region of the costal sulcus.

Case 3: Examined on February 7, 1930. This is a far-advanced case of chronic tuberculosis with predominating right-sided lesions. The heart was displaced to the right side. In the dorsal recumbent position the apex beat was not visible or palpable; in the left lateral position the heart impulse appeared in the left fifth interspace. On fluoroscopic examination the heart was seen to be displaced to the right, in the erect posture. With the patient leaning over to one side the heart readily shifted toward the lower side. (Figure 4 a & b.)

Case 4: Tuberculosis of left upper lobe. Symptoms of six weeks' duration. Sputum positive for tubercle bacilli. Physical examination on August 16, 1928: retraction of entire left side of chest with winged scapula; diminished expansion on this side. Feeble breath-sounds below 3rd rib anteriorly on left side; distant bronchial breathing in 3rd interspace; medium moist râles in 2nd and 3rd interspaces. *Fluoroscopic Examination:* Moderate-sized cavity in lower part of left upper lobe. The left lung is small and hazy; the heart is displaced to the left; the diaphragm is elevated and makes small excursions

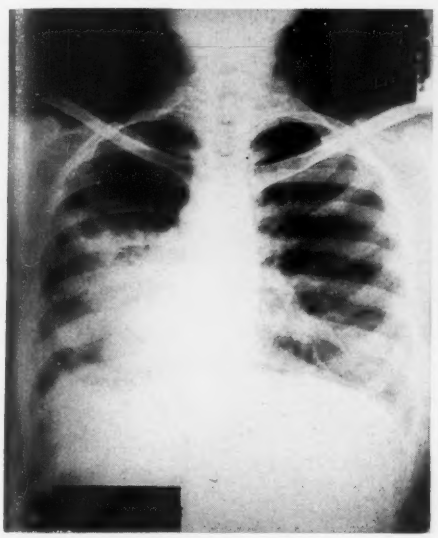


FIG. 5a

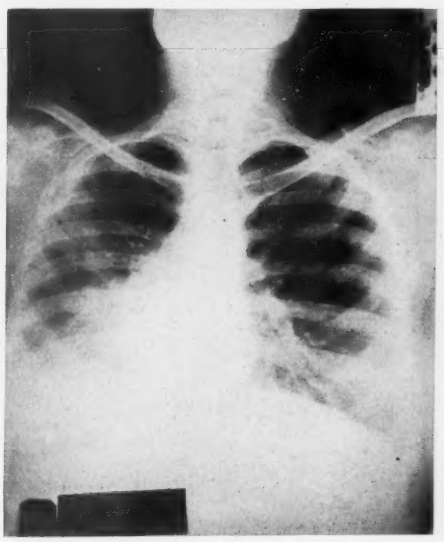


FIG. 5b

FIG. 5a. Case 4. September 27, 1928. Tuberculosis of left lung with cavity-formation. Note the tenting at the diaphragm, caused by an atelectatic lobule. The heart is displaced to the left.

FIG. 5b. Case 4. May 27, 1929. Marked improvement. The cavity has disappeared. The diaphragm is not tented any longer. The heart has returned to the normal position.

on the left side. The patient made a rapid recovery. Reëxamination on May 27, 1929: The two sides of the chest appear equal in size and the expansion is symmetrical. The breath-sounds are vesicular throughout; fine râles were present in 2nd and 3rd interspaces on left side. *Fluoroscopic Examination:* The cavity has disappeared; the heart is in the normal position. The aeration of the left lung has improved. The left dome of the diaphragm is still high and makes limited excursions. *Fluoroscopic Examination,* July 3, 1929: The left lung is nearly as large as the right; the left half of the diaphragm is at the same level as the right half, and moves freely. (Figure 5 a & b.)

Case 5. This is a far-advanced case of chronic pulmonary tuberculosis of several years' duration with atelectasis of the left lower lobe. *Physical Signs:* Marked contraction of left side of chest with obvious displacement of the heart and trachea to the left. Dulness throughout the left side, with flatness below the 4th dorsal spine to the left base, posteriorly. Absent breath-sounds over area of flatness. Bronchial breathing and whispered pectoriloquy with

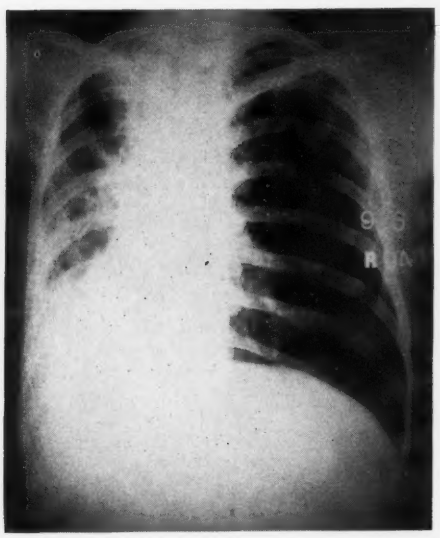


FIG. 6a

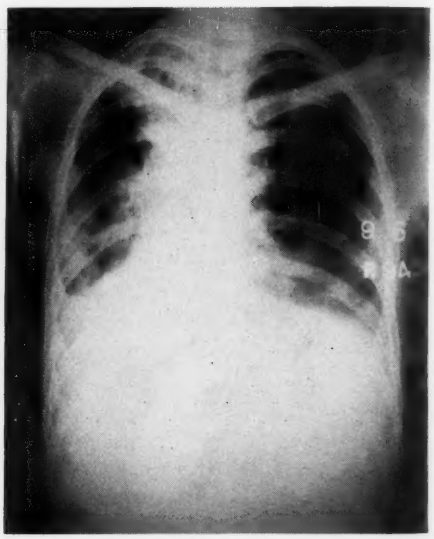


FIG. 6b

FIG. 6a. Case 5. Film taken during inspiration. The left lower lobe is airless and contracted; the trachea is distorted and displaced to the left; the heart is also displaced to the left. Between the right border of the heart and the left edge of the spinal shadow, there is air-bearing tissue belonging to the right lung which has hypertrophied and has invaded the right hemithorax. This last feature can be seen on the original X-ray films only.

FIG. 6b. Case 5. Film taken during expiration, at the same sitting as fig. 6a. The heart has moved over toward the right; the trachea has straightened out perceptibly. The normal portions of the right lung have lost much of their air, while the tuberculous lesions in the right apex as well as in the left upper lobe have increased in volume and are more transparent; the cavities in the left apex are now well outlined (paradoxical breathing). The left diaphragm is lower in expiration than in inspiration (paradoxical movement). The left border of the heart has moved away from the chest-wall.

coarse moist râles over region of left upper lobe. There are also signs of cavity-formation over the right apex. *Fluoroscopic Examination:* The left side of the chest is contracted and airless in its lower portion; the diaphragm cannot be identified on this side. The heart and treachea are displaced to the left, and the trachea is greatly distorted. The displacement of the mediastinum is increased during deep inspiration. During forced expiration the mediastinum

is seen to shift to the right (pendulum movement) and the trachea straightens out perceptibly. During inspiration the normal lung shows an increased radiability and the cavities are barely perceptible; during expiration the normal lung is seen to collapse while the cavities become distinctly larger and their air content greater. (Figure 6a & b.)

Case 6: Examined April 18, 1930. *Physical Signs:* Retraction of left side of chest with displacement of the heart to the left. Dulness and feeble breathing

FIG. 7a

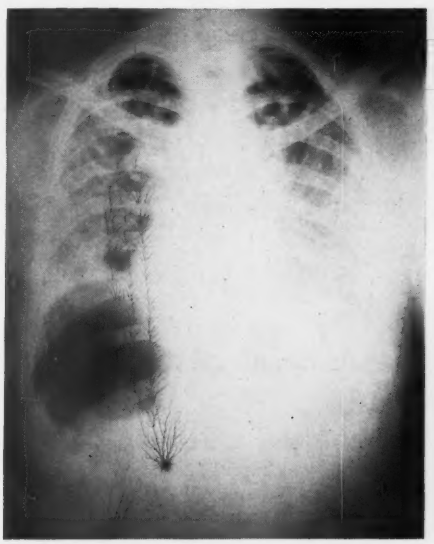


FIG. 7b

FIG. 7a. Case 6. Taken during inspiration. Tuberculosis of left lung and of right apex. During inspiration the left lung is relatively airless; the diaphragm is high and the heart is deviated toward the left.

FIG. 7b. Taken during expiration, at same sitting as fig. 7a. The air-content of the right lung has decreased, that of the left has increased; the cavities in both apices are larger and contain more air than during inspiration (paradoxical breathing). The heart has moved over to the right and away from the left chest-wall. The cavity in the left lower lobe is now well outlined.

over the region of left lower lobe. Signs of cavity-formation are noted in both lobes of left lung. *Fluoroscopic Examination:* During inspiration the heart is displaced to the left; during expiration it moves to the right for a considerable distance. During inspiration the right base is clear in contrast with the opacity of the left base; during expiration the right base becomes airless while the tuberculous left lung as well as the cavities enlarge and become transparent. (Figure 7a & b.)

SUMMARY AND CONCLUSIONS

1. Atelectasis is of common occurrence in tuberculosis and is responsible for such important signs as contraction of the chest and lung, limited mobility, feeble or absent vesicular murmur, and a decreased complemental space.

2. The small lung of tuberculosis with the displaced mediastinum and diaphragm frequently develops in spite of the absence of fibrosis and adhesions; it is due to a diminished amount of air in the affected lung and a fall in intrapleural pressure.

3. The pendulum movement of the mediastinum observed in bronchostenosis and atelectasis occurs also in tuberculosis with preponderantly unilateral distribution.

4. Parodoxical breathing accompanies tuberculous disease of the lungs; it is believed to be the cause of the characteristic râles of tuberculosis. In many cases this breathing from one lung into the other spreads the tuberculous infection.

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MASSIVE ATELECTASIS IN PULMONARY TUBERCULOSIS AND ITS TREATMENT BY ARTIFICIAL PNEUMOTHORAX[1,2]

E. E. GLENN

Lobar atelectasis or massive collapse has become a well-recognized clinical condition of the lung. It has been considered chiefly as a post-operative pulmonary complication. A review of the literature shows it quite generally agreed that lobar atelectasis is caused by bronchial obstruction, primarily. There are, however, other factors which are considered contributory, such as posture, fixation of the thorax after abdominal or thoracic operations because of pain, and decrease of, or loss of, the cough reflex because of narcosis.

Lobar atelectasis has been described by several as a complication of chronic pulmonary disease. It has been reported by Packard (1) and others as a complication of tumor of the lung because of obstruction of the bronchus by pressure from the tumor. At the Sanatorium we have seen two cases of massive atelectasis caused by bronchial obstruction due to primary carcinoma. In one of these there was an atelectasis of the left upper lobe and in the other of the entire left lung. It has been reported as a complication of pulmonary tuberculosis by Habliston (2), Packard (1), Rappaport (3), and Wilson (4). The purpose of this paper is to discuss lobar atelectasis as a complication of pulmonary tuberculosis, and especially to emphasize the importance of artificial pneumothorax in its treatment.

It is difficult to determine the exact aetiology of lobar atelectasis in all cases when it occurs as a complication of pulmonary tuberculosis. That bronchial obstruction was the aetiological factor in the case reported by Wilson (4) was shown by the patient coughing up a haemorrhagic cast. In some cases it is very likely that the condition is caused by pressure on a main bronchus by an enlarged tuberculous lymph node. A bronchus may also be obstructed by contracting scar-tissue. When the complica-

[1] Read at a meeting of the Jackson County Medical Society, Kansas City, Missouri, January 27, 1931.

[2] From the Missouri State Sanatorium, Mount Vernon, Missouri.

tion has occurred under our observation, there has always been a cavity, or cavities, with extensive disease in the upper lobe on the involved side, and with comparatively little disease in the lower lobe before the atelectasis developed. The sputum, when present, has always been thick and stringy. The condition has developed slowly. (Cases 1, 3 and 6.) These observations cause me to believe that lobar atelectasis, when occurring in pulmonary tuberculosis, is usually caused by obstruction of the bronchus to the lower lobe by thick, tenacious exudate from the upper-lobe lesion. The development of lobar atelectasis in one of our cases (case 6), in which no sputum was present, indicates that the condition may have been caused by obstruction of the bronchus to the lower lobe by pressure from a tuberculous lymph node or by contracting scar-tissue. The slow development of the atelectasis can most logically be accounted for by the bronchus, at first, being only partly obstructed. As none of our patients has been bronchoscoped and none has come to autopsy, we have no definite means of getting exact information concerning the aetiological factors.

There are no subjective symptoms which are characteristic of lobar atelectasis occurring as a complication of pulmonary tuberculosis, especially in those cases in which the onset is gradual. Dyspnoea has always been present, but usually it has not been intense. The patient may show a marked elevation of temperature, but this is not always true.

The physical findings are quite similar to those of lobar atelectasis when it appears in other conditions. The cardiac impulse usually is shifted to the involved side. There is a retraction of the interspaces and a decreased movement of the hemithorax. The breath-sounds are usually absent or greatly diminished. If present they may be bronchial in character, similar to the breath-sounds heard over the lung with lobar pneumonia. Moist râles, fine or moderately coarse, are usually present. Tactile fremitus and whispered voice are increased in some cases. Impairment of resonance is usually marked over the involved lobe.

The X-ray shows the characteristic shifting of the heart and mediastinum toward the involved side. The diaphragm on the affected side is raised, and a dense homogeneous shadow is present over the involved lobe or lobes. The lung is decreased in size. The costophrenic angle cannot be visualized at all in some cases. Because of the dense shadow in the lower lung field, obscuring the costophrenic angle, the condition has been mistaken for pleural effusion.

The diagnosis of lobar atelectasis, when a complication of pulmonary

tuberculosis, is not difficult when the possibility of the condition being present is realized. The physical and X-ray findings are quite definite. The possibility of confusing lobar atelectasis with pleural effusion has been mentioned. Lobar fibrosis may very closely simulate lobar atelectasis, and the fibrosis is most likely superimposed on the atelectasis as suggested by Packard (1). The presence of toxic symptoms with the findings of a contracted lobe should cause one to suspect atelectasis instead of fibrosis. As lobar fibrosis is probably a later stage in atelectasis, the relation of the two conditions is very close and exact differentiation is not necessary. Elkin (5) states that the taking of the intrapleural pressure is useful as a diagnostic procedure in lobar or massive atelectasis. Habliston (2) also reports a marked lowering of the intrapleural pressure. The intrapleural pressure is more negative than normal in lobar atelectasis, usually being as low as -13, -8, to -30, -20 cm. of water. If a reading of the intrapleural pressure is obtained, there can be little doubt as to the diagnosis.

It is possible for pleural adhesions to be so extensive from previous disease that the pleural space is obliterated. Also, if the lobar atelectasis has been present for several months or years, adhesions may develop because of the intrapleural tension caused by the atelectasis and the tuberculous disease in the atelectatic lobe. Because of the highly negative intrapleural pressure, the pleural surfaces will separate when light adhesions are present, which would prevent a separation under ordinary conditions. Therefore, it is important that an attempt be made to obtain a reading of the intrapleural pressure in all cases in which lobar atelectasis or fibrosis is suspected.

The literature does not give much information concerning the treatment of lobar atelectasis occurring as a complication of pulmonary tuberculosis. Rappaport (3) and Packard (1) report cases in which the collapsed lobe became aerated again without treatment. It is possible that, if the collapse has a sudden onset and the patient shows no tendency to haemorrhage, the method of Sante (6) (rolling the patient backward and forward with the involved side upward) will be effective.

Packard reports a case, in which a diagnosis of massive collapse was made in April, 1924. Artificial pneumothorax was given. Wilson (4) reports a case of right lower-lobe atelectasis, treated by pneumothorax. Rappaport (3) reports a case of left lower-lobe atelectasis treated successfully with pneumothorax. Elkin (5) states that the introduction of air into the pleural cavity of a patient with postoperative atelectasis may be

of value in relieving extreme cyanosis. Habliston (2) reports a case of chronic pulmonary tuberculosis in which a massive collapse of the left lower lobe occurred. A partial pneumothorax was induced. A relief from the symptoms was noted, and the pneumothorax was maintained with a continuous improvement of the patient. The last-mentioned author believes that the high negative intrapleural pressure is a factor underlying the symptoms of cyanosis and dyspnoea, when they occur in lobar atelectasis.

In active chronic tuberculous disease of the lungs, much absorption of toxins occurs through the pleurae because of the direction of the lymph-flow. If the visceral and parietal pleurae are separated the absorption of toxins should be less. I have stated that cavitation has been present in the upper lobe of all cases that have shown an atelectasis of the lower lobe. In all cases in which lobar atelectasis has developed under our observation, the cavity or cavities in the upper lobe have become larger as the atelectasis became more complete. I think that the enlargement of the cavity is at least partly due to atelectasis of the lower lobe putting more tension on the entire lung in its attempt to relieve the highly negative intrathoracic pressure. It is certainly difficult to understand how decrease in size of or closure of the cavity can be expected as long as these conditions exist.

All cases reported in which artificial pneumothorax has been used in the treatment of lobar atelectasis are encouraging. I believe that the above discussion gives a basis for the consideration of artificial pneumothorax as a logical form of treatment in this condition, when it occurs as a complication of tuberculous disease of the lung. Because of the critical condition of some of the patients having this complication, it is evident that treatment is necessary, if the patient is to survive. The first patient with lobar atelectasis treated by us with artificial pneumothorax showed such marked improvement that this form of treatment has been used repeatedly by us. The following are reports of cases treated at the Missouri State Sanatorium:

Case 1: R. R. H., female, age 26. Onset December, 1928, with pleurisy following influenza. Returned to work as stenographer after few days, but unable to continue work after February 1, 1929. Entered Missouri State Sanatorium April 13, 1930. At time of admission, temperature 100.6° to 104.0°, pulse 96 to 120, respirations 20–24. Complained of marked loss of weight, weakness, productive cough and anorexia. *Physical Examination: Right:* Percussion note

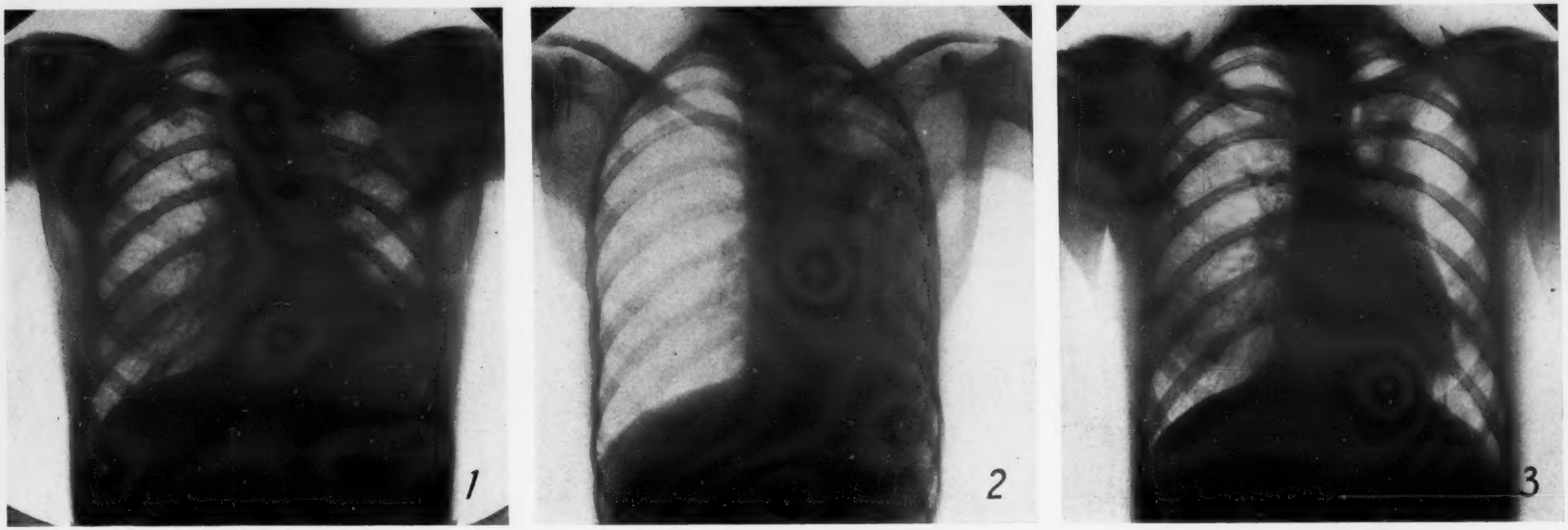


FIG. 1. Case 1. Before lobar atelectasis was fully developed. Note cavity below clavicle and position of heart and diaphragm.

FIG. 2. Case 1 after lobar atelectasis was fully developed. Note position of heart and mediastinum pulled to left. Dense homogeneous shadow in left lung. The stomach bubble indicates elevation of the diaphragm.

FIG. 3. Case 1 after induction of artificial pneumothorax. Note heart and mediastinum returned to normal position. Also normal position of left diaphragm.

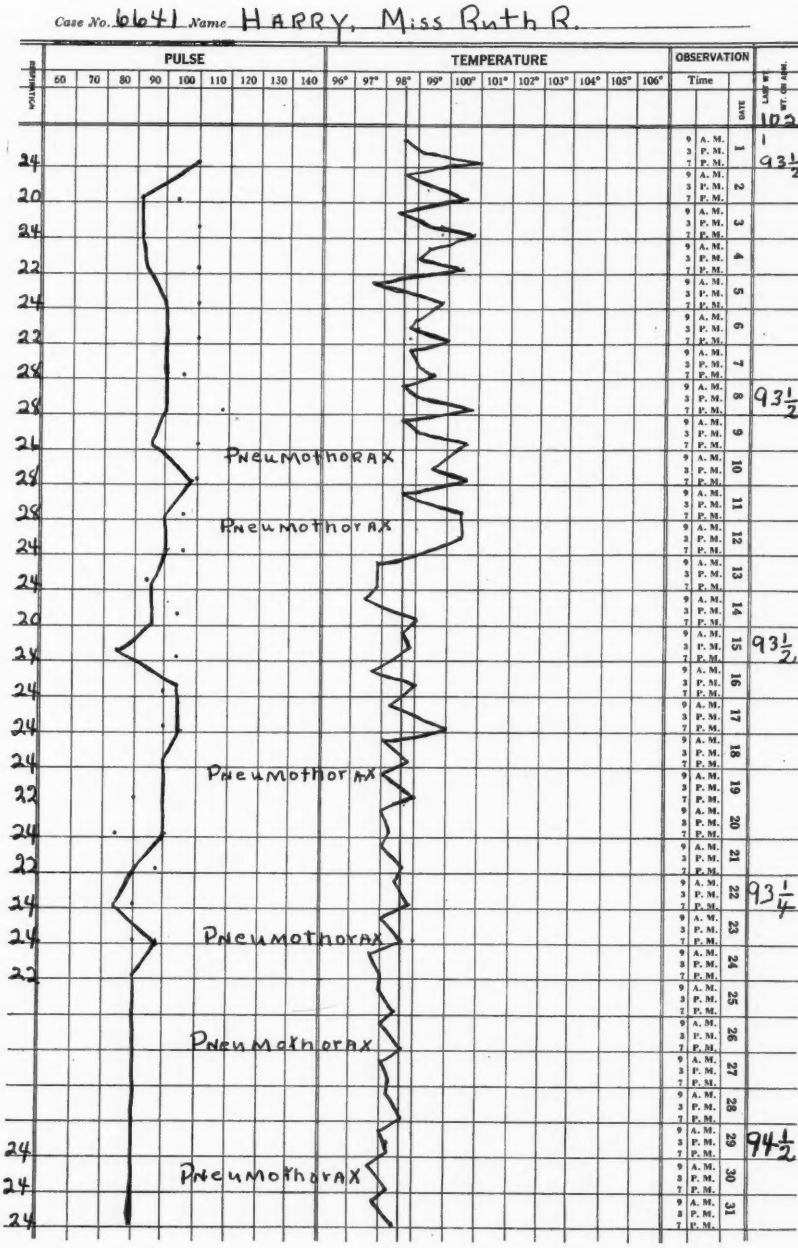


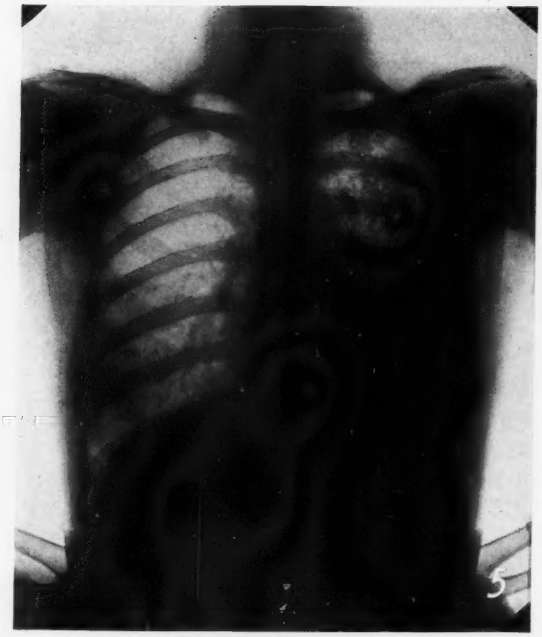
FIG. 4. Case 1. Showing temperature and pulse before and after induction of artificial pneumothorax.

impaired over upper third, whispered voice and vocal fremitus increased over same area; breath-sounds harsh in upper; no râles. *Left:* Impairment of resonance throughout, more in base anteriorly; whispered voice and vocal fremitus not transmitted; breath-sounds feeble; practically absent in base; moderately coarse moist râles throughout. Cardiac impulse slightly outside midclavicular line. Sputum thick and stringy; 30 to 40 cc. in twenty-four hours. *X-ray* (figure 1): Showed light infiltration below right clavicle, with some evidence of cavity-formation; moderately dense soft infiltration throughout left lung; cavity below left clavicle.

Patient continued to show marked elevation of temperature, lost weight, and strength decreased. *X-ray* (June 11, 1929): Showed no change in right lung; mediastinum and heart to left of normal position; left diaphragm slightly elevated and density of left lower lobe greater. *X-ray* (figure 2): July 9, 1929: Showed shadow in left lower to be more dense; cavity in left upper lobe larger; shifting of mediastinum and heart to left more marked. *Diagnosis:* Atelectasis of left lower lobe. Artificial pneumothorax instituted July 10, 1929. Intrapleural pressure on entrance, −16, −7 cm., water; 300 cc. of air introduced and closing pressure, −5, −7. Pneumothorax was continued, and satisfactory collapse obtained, as shown by X-ray (figure 3). Only small amount of thick sputum after pneumothorax; negative after October 3, 1929. Temperature normal July 13, three days after pneumothorax was begun, and no elevation above normal range was shown thereafter (figure 4). Patient rapidly gained weight and strength.

Discharged May 28, 1930, at which time condition quiescent. Advised to have pneumothorax continued.

Case 2: P. M. S., female, age 17. Onset February 1, 1929, with influenza; 13 days later temperature high and patient dyspnoeic. *Diagnosis:* Lobar pneumonia of left lung, made by attending physician. Tubercle bacilli found in sputum, and patient entered Missouri State Sanatorium, March 14, 1929, at which time febrile, dyspnoeic, and strength very poor. *Physical Examination: Right:* No abnormal findings except general comparative increase in breath-sounds. *Left:* Percussion note impaired throughout, more in base; whispered voice increased in upper and especially in axilla; breath-sounds decreased, and distant bronchial breathing in axilla; râles, moderately coarse moist, in upper, but fine moist râles predominate in base; apex impulse in 5th i.s., midclavicular line. Sputum thick, stringy, 10 cc. in 24 hours; no tubercle bacilli present, but had been found before patient entered the Sanatorium. *X-ray,* March 16, 1929 (figure 5): Showed only light infiltration in upper portion of lower lobe of right lung; soft infiltration in upper portion of left lung, with small cavity behind clavicle; shadow in lower lung field homogeneous; heart and mediastinum were to left of normal position, and diaphragm ele-



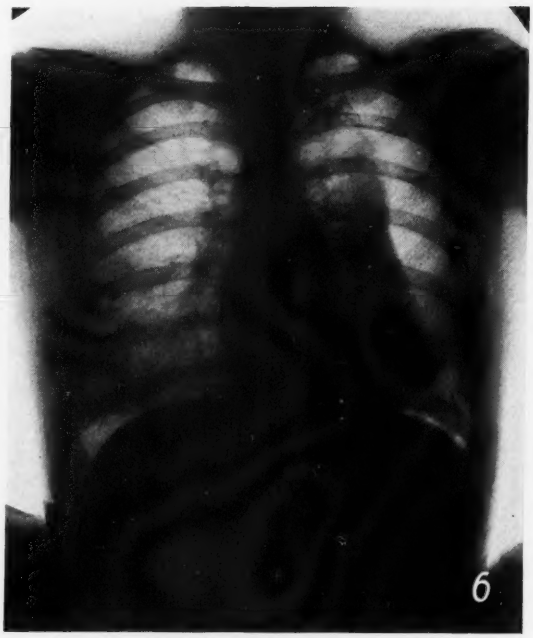


FIG. 5. Case 2. Lobar atelectasis of left lower lobe. Cavity beneath clavicle near lateral chest-wall.

FIG. 6. Case 2. Same as fig. 5 after induction of artificial pneumothorax. Good pulmonary collapse.

vated. These findings indicated the presence of massive collapse. *X-ray,* April 12, 1929: Showed no change. *April 12, 1929:* Artificial pneumothorax induced on left side. Opening intrapleural pressure was −10, −8 cm., water, and closing pressure were −7, −5, after 400 cc. of air were introduced. Patient had severe pain following treatment and 2° rise in temperature. Temperature normal next day, however, and never again showed an elevation above normal range. No sputum after pneumothorax was induced. Figure 6 is roentgenogram after institution of pneumothorax. The pneumothorax treatments were continued, and patient made rapid and steady gain in weight and strength. Discharged from Sanatorium August 29, 1930, and classified as quiescent.

Pneumothorax treatments are being continued.

Case 3: H. C., female, age 23. Onset during December, 1928, with cough. Entered Sanatorium February 28, 1929, at which time complained chiefly of productive cough and loss of weight and strength. *Physical Examination: Right:* Resonance impaired over upper fourth, whispered voice and vocal fremitus increased over apex; breath-sounds granular over apex, moderately coarse râles above 2nd thoracic spine and above clavicle. *Left:* Percussion note impaired moderately over upper half; whispered voice moderately increased over upper half; breath-sounds decreased throughout, but more in upper; moderately coarse râles above 4th spine and 7th rib; also in upper axilla. *X-ray,* March 4, 1929 (figure 7): Showed very light infiltration in right apex, and light infiltration surrounding the hilum. Left showed moderately dense infiltration throughout, with multiple cavity-formation in upper portion; haziness in base. Progress made by patient satisfactory until August, 1929, when noticed being somewhat more dyspnoeic than usual; also complained of pain in right upper thorax beneath clavicle. Sputum, 30 cc. in 24 hours; thick and stringy; tubercle bacilli present.

Physical Examination, August 31, 1929: *Right:* No important findings. *Left:* Breath-sounds decreased throughout, practically absent in base; moderately coarse râles throughout anteriorly and in upper posteriorly. *X-ray,* August 31, 1929, (figure 8): *Right:* Findings practically same as at time of admission. *Left:* Dense infiltration in lower two-thirds; this infiltration homogeneous; heart and mediastinum displaced to left and left diaphragm elevated; infiltration in the upper third less dense, but cavity below clavicle is larger. *Diagnosis:* Lobar atelectasis; artificial pneumothorax advised, and induced September 20, 1929. Opening pressure was −12, −9 cm., water; 300 cc. of air introduced, and pressure fell to −7, −6 cm., water. A few minutes after the treatment was given, patient became very dyspnoeic and collapsed; was very dyspnoeic remainder of day. Even though fluoroscopic examination immediately after the treatment showed only a small pneumothorax, at time of next treatment the lung was almost

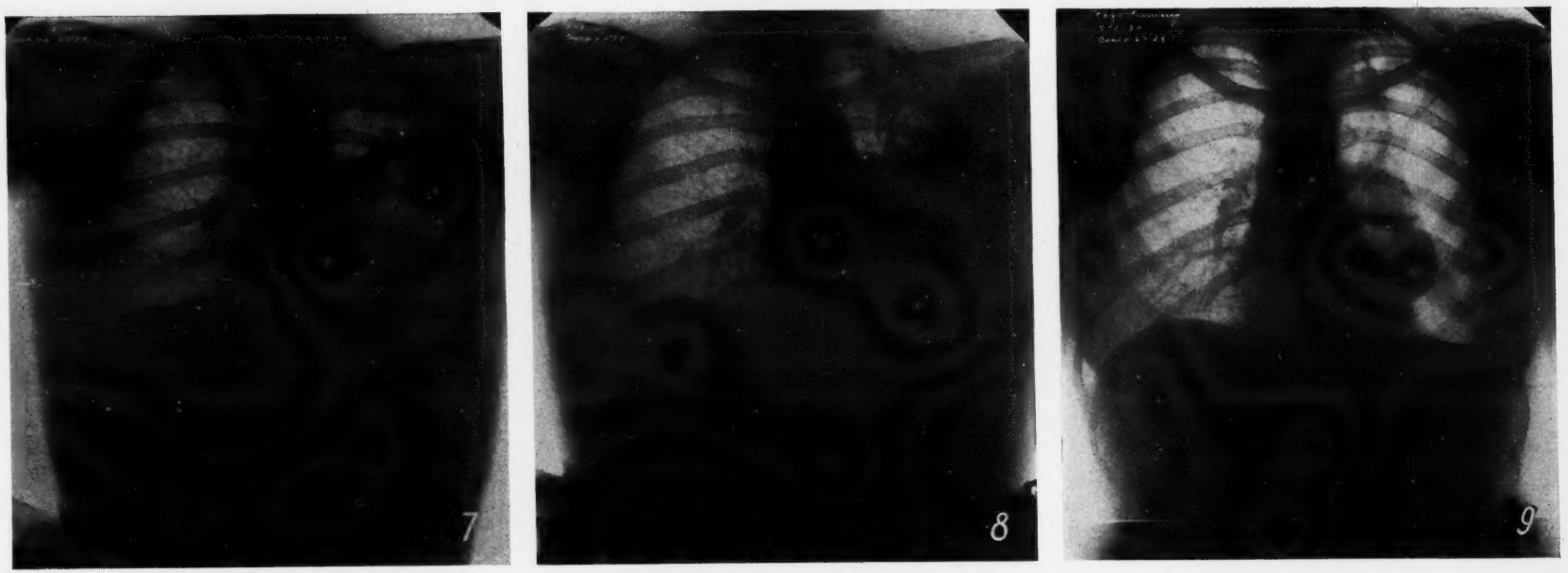


FIG. 7. Case 3 before lobar atelectasis developed. Note multiple cavity-formation in upper. Heart and left diaphragm in normal position.

FIG. 8. Case 3 after lobar atelectasis developed. Note heart to left of normal position, the dense homogeneous shadow in left lower and the cavity beneath left clavicle. The left diaphragm is much higher than in fig. 7.

FIG. 9. Case 3. Recent roentgenogram showing artificial pneumothorax. Heart and mediastinum slightly to right of normal position.

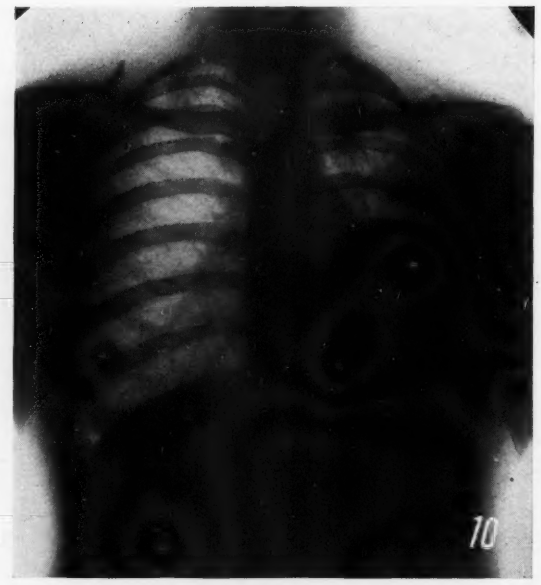
completely collapsed. The opening intrapleural pressure was +1, −1; only 50 cc. of air introduced, and closing pressure was 0, +2 cm., water. These findings indicate that the patient had a spontaneous pneumothorax following the first treatment. No sputum after pneumothorax, except for small amount occasionally, which negative for tubercle bacilli. Patient has made good progress since that time, and pneumothorax is being continued. *X-ray*, August 1, 1930, shows satisfactory collapse of lung (figure 9).

Case 4: M. S., female, age 33. Onset July, 1929, with pneumonia; told by attending physician that it resulted in unresolved pneumonia. Cough became more severe, middle of August, and September 15 expectorated blood. (During attack of illness in 1920 had had a twelve-ounce haemorrhage.) Had several small haemorrhages during December. Admitted to the Missouri State Sanatorium January 3, 1930. Continuous small haemorrhages during first week at Sanatorium. Temperature normal, but patient complained of dyspnoea. *Physical Examination: Right:* No definite abnormal findings. *Left:* Resonance impaired throughout, more in lower; whispered voice and vocal fremitus increased in upper; breath-sounds decreased throughout and practically absent in base; moderately coarse râles in upper anteriorly and lower two-thirds posteriorly. Sputum 15 cc. in 24 hours; thick; tubercle bacilli present. *X-ray*, January 11, 1930 (figure 10): Showed light infiltration in apex, with evidence of fibrosis. Left lung infiltrated throughout, moderately dense in upper; a cavity was present below clavicle; infiltration in lower lobe homogeneous and not entirely opaque; costophrenic angle visualized; heart and mediastinum were displaced to left, and diaphragm elevated. *Diagnosis:* Pulmonary tuberculosis, far advanced, with partial atelectasis of the lower left lobe. Artificial pneumothorax induced January 21, 1930. Opening intrapleural pressure −15, −12 cm., of water; 300 cc. air were introduced, after which intrapleural pressure was −11, −7 cm., water. *X-ray*, February 7, 1930: Showed good collapse of lung (figure 11). Pneumothorax continued, and progress made by patient satisfactory. Did not have haemoptysis after induction of pneumothorax, nor raise any sputum.

Discharged September 14, 1930, and advised to have pneumothorax continued. A recent report indicates satisfactory progress.

Case 5: G. L., female, age 18. Onset June, 1929, with cold, productive cough and weakness. Went to a western state; treated by physician with experience in chest work. Told most of her disease was in left lung, but could not take pneumothorax because of adhesions. Made some improvement during time in West, but still bedridden and showed daily rise in temperature at time admitted to Sanatorium, August 5, 1930.

Had two-ounce haemorrhage day of arrival at Sanatorium. Temperature



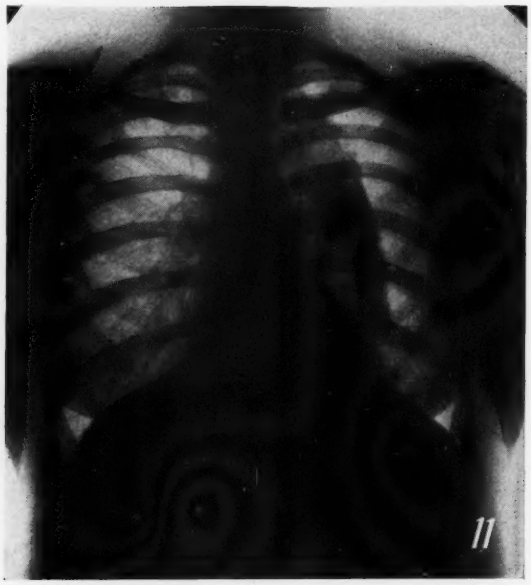


FIG. 10. Case 4. Atelectasis of left lower lobe. Cavity beneath clavicle difficult to visualize but could be outlined from X-ray negative.

FIG. 11. Case 4. Same as fig. 10 soon after induction of artificial pneumothorax. Note complete pulmonary collapse and the return of the heart and diaphragm to normal position.

range 98.8° to 101.4°. Had aphonia, which laryngeal examination showed to be due to laryngeal tuberculosis, not very active. *Physical Examination: Right:* Slight impairment of resonance in the paravertebral space; whispered voice slightly increased. *Left:* Resonance impaired throughout, more in lower half; whispered voice increased throughout; breath-sounds bronchial; moderately coarse râles throughout. Sputum 120 cc. in 24 hours, bloody and thick; tubercle bacilli present. *X-ray*, August 12, 1930 (figure 12): Light infiltration in midportion of lung; annular shadow at level of 3rd rib anteriorly, which may not be due to cavity-formation. Left lung shows moderately dense infiltration throughout upper two-thirds; infiltration in lower third, dense and homogeneous. Heart and mediastinum displaced to left; left diaphragm higher than right. *Diagnosis:* Pulmonary tuberculosis, far advanced, with lobar atelectasis of left lower lobe. Artificial pneumothorax induced on left side, August 21, 1930. Opening pressure −18, −15; 300 cc. of air introduced, and pressure fell to −12, −7; 300 to 400 cc. of air introduced on three different occasions. Sputum decreased to 10 cc. in 24 hours after pneumothorax, but tubercle bacilli are still present. *X-ray*, August 27 (figure 13), 6 days after first pneumothorax treatment: showed pneumothorax on left side; the cavity in upper did not collapse because of adhesions; lower lobe readily separated from the parietal pleura; heart moved toward normal position and diaphragm lowered. Patient has gained strength and weight; temperature has not been above 99.2°. Recent X-ray shows cavity in upper left somewhat smaller. Pneumothorax being continued.

Case 6: M. R., female, age 19. Onset early part of 1927, with cold, followed by cough, weakness and loss of weight. Entered Missouri State Sanatorium April 14, 1930, at which time complained of dyspnoea on exertion and pain in left side. Coughed very little; no sputum. Temperature 98° to 98.6°; pulse 86 to 92. *Physical Examination: Right:* No abnormal findings. *Left:* Percussion note impaired moderately over upper half; whispered voice and tactile fremitus increased in same area; moderately coarse moist râles over upper half, anteriorly and posteriorly. *Roentgenogram* (figure 14), April 16, 1929: *Right:* No important abnormalities. *Left:* Infiltration throughout, more dense in upper third, where small multiple annular shadows were present; infiltration in base homogeneous, and heart and mediastinum to left of normal; left diaphragm higher than right. *Diagnosis:* Pulmonary tuberculosis, far advanced, with partial atelectasis of left lower lobe. Artificial pneumothorax suggested, but, because of the few symptoms shown by the patient, not urged. Examination, July 22, 1930, indicated condition practically same as when admitted. *Physical Examination*, October 13, 1930: More suppression of breath-sounds in left lung, especially in lower third; moderately coarse moist râles still present in upper portion of lung; the cardiac impulse to left of normal.

FIG. 12. Case 5. Lobar atelectasis of the left lower lobe. Note large cavity in apex and the heart and mediastinum to the left of normal position; also the dense homogeneous shadow in the left lower.

FIG. 13. Case 5. Same as fig. 12 soon after induction of artificial pneumothorax. Note separation of lower lobe from parietal pleura and return of heart and diaphragm to normal position. Apical cavity is not collapsed because of adhesions.

Roentgenogram (figure 15) October 14, 1930: Showed density of lower left lobe increased; diaphragm was in about same position as when previous roentgenogram was made; heart and mediastinum had moved further to left; areas of rarefaction still present in upper left, and one was distinctly larger. Because of these findings decided to induce artificial pneumothorax. *November 7, 1930:* 300 cc. of air introduced into left pleural cavity; opening pressure −15, −9 cm., water; the closing pressure −9, −5 cm., water.

Roentgenogram (figure 16): November 14, after four injections of from 300 to 500 cc. of air: showed satisfactory collapse. Heart and mediastinum in normal position, and left diaphragm now lower than right. Patient doing nicely, but enough time has not elapsed to determine ultimate results of treatment.

Case 7: E. M., male, age 28. Onset gradual; loss of appetite, weakness, cough and expectoration first noticed, January, 1928. Entered Missouri State Sanatorium June 26, 1929. At this time complained of pain in left lower thorax, dyspnoea, weakness, cough and expectoration. Temperature 98° to 99.4°; pulse 70 to 90. *Physical Examination: Right:* Percussion note impaired slightly in upper; whispered voice slightly increased in same area; breath-sounds increased; no râles. *Left:* Percussion note impaired over upper two-thirds posteriorly and upper third anteriorly; whispered voice and vocal fremitus increased in upper half; moderately coarse moist râles throughout, more in upper. Sputum gray and thick; 180 cc. in 24 hours; tubercle bacilli present. *X-ray* (figure 17): June 27, 1929: *Right:* Small annular shadow at level of 7th rib posteriorly, near hilum, which not visualized on later films, not believed to be due to cavity-formation; lung field otherwise clear. *Left:* Moderately dense infiltration throughout; two annular shadows below clavicle in upper third, each 4 cm. in diameter; left diaphragm slightly higher than right, and heart slightly to left of normal. These findings caused us to suspect beginning lobar atelectasis. Artificial pneumothorax advised for this reason and because disease was unilateral in character. Treatments were refused by patient. Twenty-one days after admission patient became dyspnoeic, and suffered severe pain in left lower thorax. Temperature rose to 105°, and pulse increased correspondingly.

Physical Examination: Breath-sounds absent in extreme base and greatly decreased throughout left lung; moderately coarse and fine moist râles numerous in left lower portion of lung. *Roentgenogram*, July 27, 1929: Showed infiltration in lower left lung to be more dense and to have homogeneous appearance. Because of these acute symptoms patient willing to have artificial pneumothorax induced. Attempt to enter pleural cavity made July 27, 1929, and several times thereafter; pleural space apparently completely obliterated by adhesions. *Roentgenogram* (figure 18), August 26, 1929: No findings distinctly different from those present immediately after atelectasis occurred,

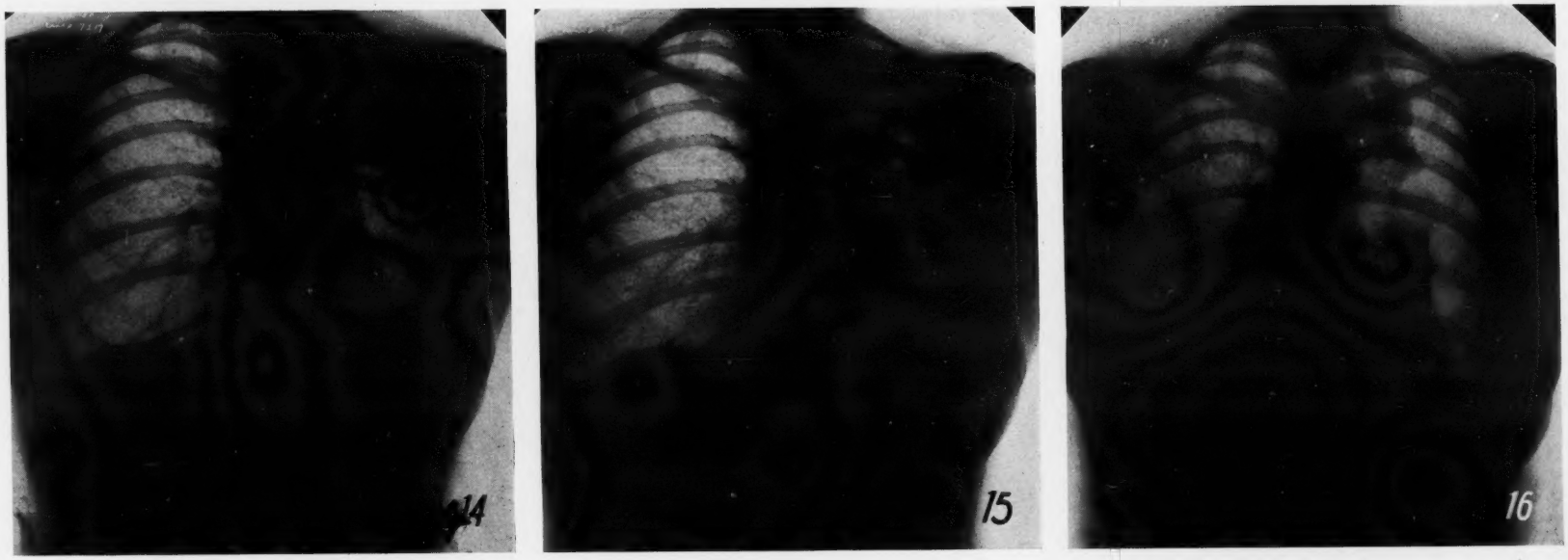


FIG. 14. Case 6. Partial atelectasis of left lower lobe. Note heart and mediastinum to left of normal position and elevation of left diaphragm. The atelectasis is most marked in the extreme lower portion of the lower lobe.

FIG. 15. Case 6. Same as fig. 14 six months later. Lobar atelectasis fully developed. The heart and mediastinum are pulled to the left and the diaphragm shows more elevation. Cavity can be visualized at level of third rib anteriorly.

FIG. 16. Case 6. Same as fig. 15 soon after induction of artificial pneumothorax. Note return of the heart, mediastinum and diaphragm to normal position; also the satisfactory pulmonary collapse.

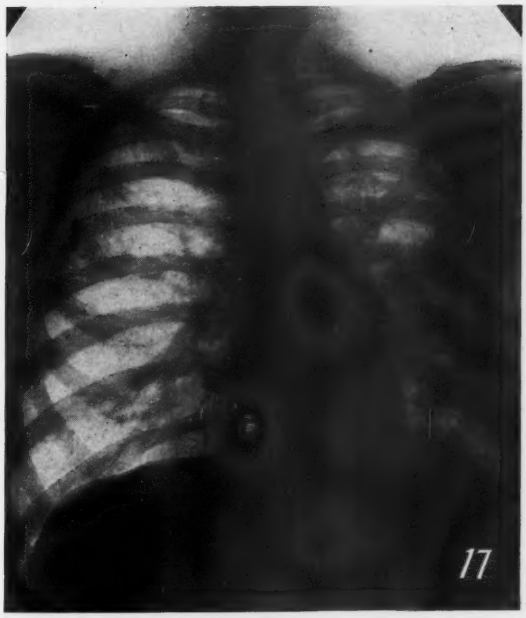


FIG. 17. Case 7. Partial atelectasis of left lower lobe. Note large cavity beneath clavicle. The heart is to left of normal position and the left diaphragm is higher than the right.

FIG. 18. Case 7. Atelectasis of left lower lobe more marked than is shown in fig. 17. The cavities in the upper left lung are larger than shown in fig. 17. The left lower lobe is more dense and has a homogeneous appearance.

except that cavities in left upper lobe are larger; shows, however, that heart is very little to left of normal, but left diaphragm greatly elevated.

At this time spread of disease into right lung began, and within few months became extensive. Patient never showed improvement, and was discharged October 22, 1930, unimproved.

This case is reported to illustrate the need of treatment in lobar atelectasis and to show the progress of a patient who, with this condition, could not be given artificial pneumothorax because of adhesions.

COMMENT

Seven cases of lobar atelectasis reported in this paper have been of the left lower lobe. Three cases, reported by Packard (1), of lobar atelectasis associated with pulmonary tuberculosis, and the cases reported by Rappaport (3) and Habliston (2) were of the left lower lobe also. The case reported by Wilson (4) was of the right lower lobe. Douglas (7) has treated a case of right lower-lobe atelectasis successfully with artificial pneumothorax, but the patient had many haemorrhages before the condition developed, and Douglas believes it quite possible that the aetiological factor was a haemorrhagic bronchial cast as in the case reported by Wilson. To say the least, it seems that, when lobar atelectasis occurs as a complication of pulmonary tuberculosis, the left lower lobe is most often involved.

One must realize that lobar atelectasis, developing as a complication of pulmonary tuberculosis, does not often give the same symptomatology as when it develops as a postoperative complication. For the symptoms of dyspnoea and cyanosis to appear it seems necessary for the bronchial obstruction to be completed without delay. However, I believe that we are justified in terming all cases *lobar atelectasis* which give objective evidence of an atelectatic or airless lobe, regardless of how slowly the signs have developed. It does not appear that lobar atelectasis, when a complication of pulmonary tuberculosis, is a simple process. In other words, the lobe once so affected seldom reëxpands. The lobe becomes involved in the tuberculous process most likely from the infected matter which obstructs, or partly obstructs, the bronchus in much the same way as Coryllos (8) suggests that lobar pneumonia develops.

We have discussed the fact that the negative intrapleural pressure becomes more negative when lobar atelectasis occurs. It is this negative pressure or tension which causes the diaphragm to rise and the heart and mediastinum to move toward the involved side, to occupy the space

which was filled by the aerated or expanded lobe. If the diaphragm and mediastinum were rigid like the bony wall of the thorax, the negative pressure would be enormous, if one or more lobes of the lung were to be reduced greatly in size by becoming atelectatic. A somewhat similar state of affairs exists when one attempts to allow a lung to expand which has been compressed by pneumothorax and the walls of the pleural cavity have been made rigid by fluid or pus within it. The fibrosis does not allow the mediastinum or diaphragm to move and the lung cannot expand for the same reason. The intrapleural pressure becomes exceedingly negative.

Let us consider a hypothetical case, in which the lung has been collapsed by pneumothorax and the walls of the pneumothorax cavity have become rigid, but in which the lung is not kept from expanding by fibrosis of the visceral pleura or of the pulmonary parenchyma. If injections of air are discontinued, the air present in the pleural cavity will be absorbed and the intrapleural pressure become correspondingly reduced. The high negative pressure will then be reduced by atmospheric pressure entering the alveoli of the lung through the bronchi. The lung will be forced to reëxpand rapidly, and, if cavities have been present before the lung was collapsed and have not been completely healed while the lung was collapsed, they will be reopened by the effort the lung is making to reduce the negative intrapleural tension. The same principles apply to the lung in which one or more of the lobes are atelectatic. Lung tissue only is between the atmospheric pressure and the highly negative intrapleural pressure or tension. As stated before, in all cases of lobar atelectasis in pulmonary tuberculosis, which have been reported, there has been extensive tuberculous disease in the involved lung with cavity-formation, practically always in the upper lobe. The air entering the lung through the bronchi at atmospheric pressure will strive to neutralize the highly negative intrapleural pressure, and, in so doing, will have a tendency to enlarge cavities present in the diseased lung, and perhaps produce other cavities in soft caseous areas. This more or less theoretical consideration is borne out in our cases, which have shown enlargement of cavities and the appearance of others, as the lobar atelectasis develops. Because of the nature of lobar atelectasis when occurring in pulmonary tuberculosis, as discussed above, artificial pneumothorax or surgical collapse of the thoracic wall seems to be the only way of combating the ill effects produced by the condition. Artificial pneumothorax is, of course, the most logical. Artificial pneumothorax also separates the visceral from the

parietal pleura, and thereby greatly decreases the absorption of toxins. At times this seems to be a great factor, especially in patients who are very toxic, as is illustrated by cases 1 and 2 of this series. The heart and mediastinum are also returned to normal position by the induction of pneumothorax, but in our cases we do not feel that this has been of great importance.

CONCLUSIONS

1. Seven cases of lobar atelectasis, or massive collapse, of the left lower lobe, occurring as a complication of pulmonary tuberculosis, are reported.

2. Six of these cases have been treated by artificial pneumothorax and all have been benefited; in at least two cases the prognosis has been changed from unfavorable to favorable by this treatment.

3. One patient (case 7) could not be given artificial pneumothorax because of the pleural space being obliterated by adhesions.

4. Lobar atelectasis, when a complication of pulmonary tuberculosis, is not difficult to recognize if the likelihood of its being present is realized.

5. Artificial pneumothorax is believed to be the logical treatment for this condition.

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FAT THERAPY IN EXPERIMENTAL TUBERCULOSIS OF RABBITS[1]

SAMUEL A. LEVINSON

From the very earliest times of recorded medical effort phthisiotherapy has played an important rôle. The ancient physician, who wore the cloak of the priest-physician, had a broad experience of folk medicine, and this forms at times the basis of empirical medicine. As far as tuberculosis is concerned it seems as if the treatment was in the realm of dietotherapy, for the most favorable results were obtained from the diets rich in fats. The old empirical conception, that the absence of fats in the diet appears to influence tuberculosis unfavorably, was recently mentioned by the medical authorities of Central Europe for the war and postwar period.

It might not be out of place to mention rather briefly the therapeutic usage of fats and oils among the ancients. The Egyptian papyri mention the use of rape-oil, the Hindoo recommends a liberal diet of meat together with vegetable and animal oils in the treatment of phthisis. The Greeks, aside from the hygienic treatment, employed a liberal milk diet in the therapy of tuberculosis. Olive oil was employed by the teachers of the Salerno school in the treatment of consumption.

This form of treatment, used by the ancients, continued in the folk medicine of Europe, and the employment of fats, milk of goats and asses, dog fat, and numerous oils reëstablished the fat regimen as a therapeutic measure in tuberculosis. This procedure has been changed more or less, so that a modified form is used at the present time.

It is somewhat logical to assume that when an agent is employed in the treatment of a disease from the very earliest times to the present, and although no complete beneficial result could always be obtained, it remains nevertheless a fact that this form of therapy must have had some intrinsic value. Aside from the observation that fats are present in the ordinary diet, we must not lose sight of the fact of their nutritive value and that they also have therapeutic benefits. We find that in 1824 cod-

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liver oil was introduced in the diet of the consumptive patient. Although the diet was of a high protein type, Brehmer advised against its use, and introduced a well-balanced diet, and at the same time one rich in fat. This was followed by a period of fat-rich feeding (Detweiler) and of overfeeding until a reaction followed against the use of this form of treatment and swept into disrepute methods and elements of possible beneficial value.

Regarding fats as food, Schroeder quotes Weigert as having proved that overfeeding swine with fat increases their resistance to tuberculosis, and Vogt as having seen greater immunity to tuberculosis in fat-nourished children. Since fatty foods are not taken persistently the most important substitute is codliver oil, to which has been ascribed an almost specific influence in scrofula and tuberculous diseases. It may be noted that in this earlier work the codliver oil was given, not only on account of its food value as a fat, but also with the idea that it increased resistance to the disease.

Probably some of the beneficial effects of codliver oil may be due to the vitamine content. Recent studies on the specific therapeutic effect of codliver oil in rickets have brought out the remarkable fact that codliver oil and heliotherapy have identical effects, both on the progress of the disease and on the metabolism of the subject, there being an accelerated rate of recalcification and increase in the inorganic phosphates of the blood (Hess). Since heliotherapy and codliver oil both benefit tuberculosis, especially the surgical forms, it seems probable that their influence here may be similar to their influence in rickets.

In recent years avenues of approach along the lines of various forms of therapy in tuberculosis have been opened, and all of these seem to have as their fundamental basis the relation of fats and lipoids to the therapeusis of the disease. As a result of clinical observations, fats have been employed in the diet because of their beneficial value; others, working along investigative lines, particularly in the field of immunology in an effort to discover fat antibodies, also the chemical study of the tubercle bacillus (Wells, Long), have started a number of investigators to approach the study with the conviction that in fat metabolism and lipolytic activity there must be found the underlying processes that are involved in the mechanism of recovery from tuberculosis.

Apart from the above-mentioned commonly used oils, cholesterols have played a prominent rôle in lipotherapy in tuberculosis. The literature of recent years contains references to the antihaemolytic and antitoxic

properties of cholesterol. Kulz employed cholesterol in anaemias. Lemoine and Gerard used cholesterol empirically in tuberculosis. Valois was of the opinion that in tuberculosis resistance and improvement were paralleled by an increase in the cholesterol content of the blood while in patients who did not improve the cholesterol content of the blood was decreased. Valois's opinion that patients treated with cholesterol showed a distinct clinical improvement was corroborated by MacDonald.

Serona used a mixture called *luteine*, which consisted of cholesterol with palmitic and oleic acids, while Coleschi employed a preparation of cholesterol dissolved in oil of mandarole, with favorable results in tuberculosis. The effect of overfeeding cholesterol and its possible harmful effect on the organism was also considered.

Dewey has published experimental data concerning the feeding of cholesterol to animals. In the tuberculosis of experimental animals Grinew reported that changes in the lipoid content of organs are most marked in the lungs, liver, spleen and bone-marrow, a reduction in the total amount of lipoids being most constant, with rearrangement in the proportions of lecithin and kephalin. The fact observed by Valois that, with improvement in the clinical condition in tuberculosis, a coincident increase in the cholesterol of the blood is to be observed, must not be considered as being peculiar to his disease alone, for the studies of Jolly and Mondelange have indicated that in typhoid and paratyphoid fevers the cholesterol index of the blood is very low during the period of greatest activity of the disease and increases progressively with the recovery of the patient.

In spite of the favorable reports of the use of cholesterol in tuberculosis, more recent studies would question the usage of cholesterol, despite the detoxicating effect cholesterol has on certain true toxins and alkaloids. In tuberculous women during the period of menstruation there is a distinct fall of cholesterin. In the premenstrual state the cholesterin is usually increased. At the time of menstruation the total free fatty acids in the blood are increased while the lecithin remains unchanged (Kaufman and Muehlbok). Salomon and DePotter have shown that the cholesterol content of the blood increases in normal pregnancy, while in progressing tuberculosis it falls below normal. The cholesterolaemia was low in the progressive cases and high with a nonactive process.

In experimental studies with cholesterol in tuberculosis Luden observed the cholesterol content of the blood under the influence of feeding and came to the conclusion that a diet which reduces the blood-cholesterol

increases the lymphatic resistance. French investigators are of the opinion that cholesterols may have some influence in lowering the temperature in infectious diseases and are therefore of some value, while other observers (Sisto) find no parallelism between the degree of febrile reaction and hypercholesterolaemia.

Lecithin has been introduced in the treatment of tuberculosis, and Sieber and Metalnikoff are of the opinion that lecithin increases antibody production in tuberculosis. Momose noted that animals treated with lecithin became more resistant to tuberculosis.

In our present investigation we were primarily concerned with the effect of cholesterol feeding on the tuberculous process, and in studying the increase in the weight of the animals with this form of treatment. Together with a chemical analysis of the blood for cholesterol, cholesterol esters, and fatty acids, a histopathological examination was made of the different organs, and a polariscopic examination of the tissues for double refracting fats. This latter was reported in a previous communication (Jaffé and Levinson).

EXPERIMENTAL OBSERVATIONS

To determine the amount of oil and the kind of oil necessary that will not produce inflammatory changes in the gastric mucosa (gastritis), the following preliminary experiment was performed: From a large series of rabbits and guinea pigs, which were divided into smaller groups, peanut oil, sperm oil, olive oil, and cotton-seed oil were fed by stomach-tube; some animals were fed every day, others every other day; some were fed once a week, and others twice a week. The amount of oil fed by stomach tube was 2–3 cc. for guinea pigs and 5–10 cc. for rabbits. This feeding was carried out over a long time and the animals that remained alive were killed. It was found at autopsy that, with the exception of the cotton-seed oil, there resulted a gastritis from the feeding of the other oils. As a result of this observation we have employed cotton-seed oil directly and as a vehicle for other substances used in feeding. As will be noted later, we have fed cotton-seed oil daily to rabbits over a period of 6 months without any gastric or intestinal irritation.

The next experiment consisted of feeding plain cotton-seed oil, cholesterol in cotton-seed oil, and egg-yolk, to a large series of rabbits. At first blood was drawn from all the rabbits to determine the average normal content of cholesterol, cholesterol esters, and total fats in whole blood and in blood plasma. The technique used is that described by Bloor, using

the saponification method, and we added kaolin to the alcohol-ether mixture to remove any trace of coloring matter that may interfere with the final reading of the results in the colorimeter. The animals were bled at regular intervals during feeding and after the injection of the tubercle bacilli, and similar determinations were made on the blood and plasma; a final determination of the cholesterol, cholesterol esters, and fatty acids was made on the whole blood and plasma just before the animals were killed. A determination of the weights of the animals was also recorded, first the normal control and later at regular weekly intervals.

The diet for the rabbits was the same at all times, consisting of grass, oats, carrots and water.

The feedings of plain cotton-seed oil, cholesterol in cotton-seed oil, and egg-yolk were given by stomach-tube in the following manner: Each group consisted of 6 animals. Group 1 were control animals which received no feedings and were not injected with tubercle bacilli. Group 2 were control animals, injected with tubercle bacilli but not fed with oil, cholesterol, or egg-yolk. Group 3 received plain cotton-seed oil, 5 cc. daily, by stomach-tube, but were not injected with tubercle bacilli. Group 4 received cotton-seed oil daily and were also injected with tubercle bacilli. All animals injected with tubercle bacilli received 20 mgm. of bovine tubercle bacilli (nos. 6, 30, 18) in salt solution, intravenously. The injections were given 2 months after the animals received the feedings, and the latter were continued to the end of the experiment. Group 5 received 0.25 gm. cholesterol in 5 cc. cotton-seed oil by stomach-tube daily, but were not injected with tubercle bacilli. Group 6 received the same feedings as group 5 but were injected with tubercle bacilli. Group 7 received an egg-yolk daily by stomach-tube, but were not injected with tubercle bacilli, while group 8, receiving the same feeding, were injected with tubercle bacilli.

In the tabulation of our experimental observations it will be noted that, as far as the cholesterol content of the blood and plasma is concerned, no marked difference could be observed. This seems to be in accord with the experimental findings of other investigators. As far as the cholesterol esters are concerned in the human being, the plasma cholesterol esters are slightly higher than in the red cells. In the tabulation of our results we have chosen a representative series of animals, and the findings agree with the other experiments which we have performed as preliminary to this one. As a check the same experiment has been repeated four times.

In the blood-chemistry reports, as noted in the various protocols, each sample of blood was examined in duplicate.

Cholesterol: Table 1 shows the cholesterol findings in the whole blood. It will be noted that the average normal cholesterol content of the whole

TABLE 1

*The cholesterol, cholesterol esters and fatty acids of the whole blood and serum in control rabbits and rabbits injected with tubercle bacilli**

NUMBER		CONTROL (2 MOS.)			AFTER TUBERCLE-BACILLUS INJECTIONS (4 MOS.)			AFTER FAT FEEDING (6 MOS.)		
		Cholesterol	Esters	Fats	Cholesterol	Esters	Fats	Cholesterol	Esters	Fats
		mgm.	*mgm.*	*mgm.*	*mgm.*	*mgm.*	*mgm.*	*mgm.*	*mgm.*	*mgm.*
34	Blood	66.6	22.2	244.2	138.2	83.3	222	115.3	104.1	266.4
	Serum	33.3	22.2	199.8	91.6	83.3	—	138.8	104.1	355.2
35	Blood	36.6	too faint	244.2	91.63	83.3	177.6	138.8	104.1	266.4
	Serum	33.3	too faint	177.6	91.63	83.3	177.6	104.1	104.1	310.8
25	Blood	66.6	too faint	177.6	71.3	39.984	310.8	138.8	104.1	444.4
	Serum	59.9	too faint	177.6	66.66	39.984	355.2	138.8	104	444.4
28	Blood	73.326	33.33	222.2	266.56	36.65	222.2	138.8	104.1	155.4
	Serum	66.66	35.52	222.2	233.24	49.98	266.4	138.8	104.1	155.4
32	Blood	99.99		266.4	199.92	299.88	444	832.1	472.1	310.8
	Serum	79.99		266.4	266.56	—	532	832.1	416	355.2
31	Blood	73.32	28.886	244				833.1	377.6	488.4
	Serum	33.33	35.552	199				555.4	370.2	577.2
41	Blood	79.99	33.33	177	333.24	222.2	310.8	519.3	297.1	310.8
	Serum	73.32	35.55	155	333.24	222.2	266.4	694.2	360.9	488.4
37	Blood	67.82	39.99	133.2	230.5	222.2	266.4	230.4	138.8	310.8
	Serum	67.82	39.99	133.2	230.49	244.4	222.2	277.6	124.9	310.8

* The numbers of the rabbits on this table correspond with those rabbit numbers on chart 1.

blood of rabbits is between 80–90 mgm. per 100 cc. of blood. At the end of 2 months 20 mgm. of bovine tubercle bacilli (nos. 6, 30, 18) were injected intravenously, with the exception of those animals which were

used as feeding controls. Rabbits 34 and 35 were tuberculous control animals, and the examination of the protocol shows that the cholesterol content increased after the tubercle-bacilli injection to 138 mgm. At the end of the fourth month, in rabbit 34 there was a slight decrease in the cholesterol content of the blood after tubercle-bacilli injection, and this is of marked significance as it seems to occur in all the animals, and this phase of the question will be discussed later. The feeding of plain cotton-seed oil to rabbits (no. 25) which were not injected with tubercle bacilli resulted in a continual rise of the cholesterol, so that at the end of the experiment the whole blood contained about 138 mgm. per 100 cc. Rabbit 28 was fed with plain cotton-seed oil for two months and then injected with tubercle bacilli. At the end of the fourth month the cholesterol content had increased to 268 mgm., and toward the end of the experiment it had dropped to 138 mgm. per 100 cc. of blood. From this experment it will be noted that the greatest rise in cholesterol followed the injection of tubercle bacilli, and the drop in the cholesterol content in animals fed with plain cotton-seed oil and injected with tubercle bacilli was always greater than the average normal cholesterol content of the animal.

The feeding of egg-yolk to rabbits (no. 41) without tubercle-bacilli injection resulted in a continual rise of the cholesterol content, so that at the end of 4 months there were 334 mgm. and at the end of the experiment 519 mgm. per 100 cc. of blood. The animals receiving similar feedings, but also injected with tubercle bacilli (no. 37), did not show a very great increase in the cholesterol content as compared with the egg-yolk control, and at the completion of the experiment the cholesterol content was practically the same, 232 mgm. per 100 cc. of blood. In this experiment the cholesterol content increased after the tubercle-bacillus injection but no appreciable increase was noted toward the end of the experiment.

The greatest increase in cholesterol content of the blood was noted in the animals which were fed cholesterol in cotton-seed oil (no. 32). In the cholesterol-fed control animal the increase at the end of the fourth month was 278 mgm., and at the end of the experiment the cholesterol content was 832 mgm. per 100 cc. of blood. The animals receiving similar feedings, but also injected with tubercle bacilli (no. 30), showed a marked increase in the cholesterol content, following the injection of the organisms, to 488 mgm., but, as the feeding was continued, the cholesterol content of the blood was only slightly increased over the latter figure to 555 mgm. per 100 cc. of blood. From the examination of the protocols

of the animals, fed with egg-yolk and cholesterol and also injected with tubercle bacilli, it seems as if the injection of these organisms has an inhibitory effect on the further increase in the cholesterol content of the blood.

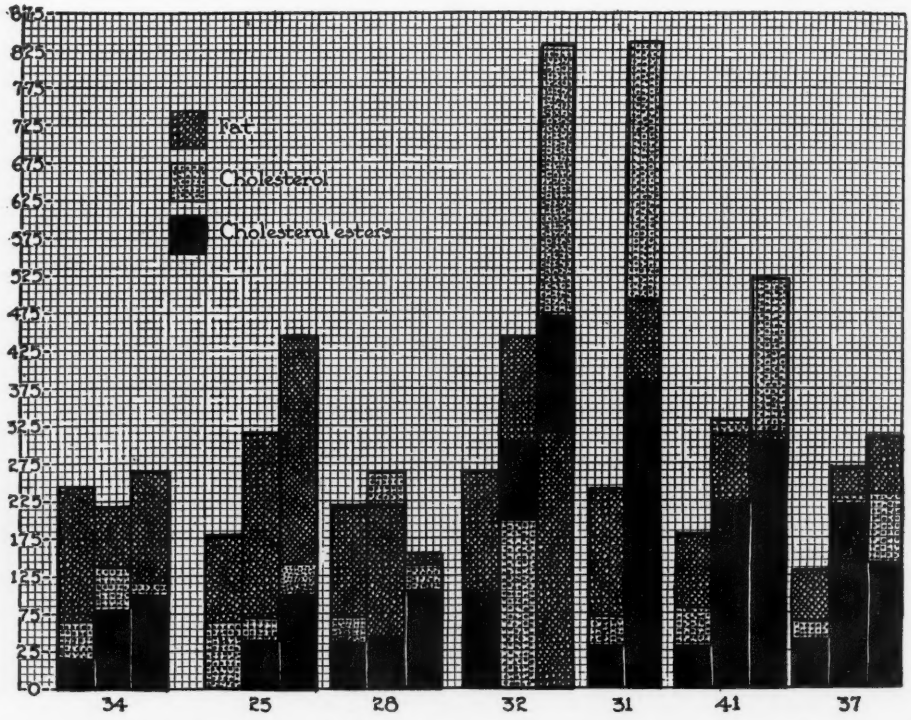

CHART 1. LIPOID RATIOS OF THE WHOLE BLOOD IN CONTROL AND TUBERCULOUS ANIMALS

34. Control tuberculous rabbit.
25. Cotton-seed-oil control.
28. Cotton-seed-oil plus injection of tubercle bacilli.
32. Cholesterol control.
31. Cholesterol plus injection of tubercle bacilli.
41. Egg-yolk control.
37. Egg-yolk plus injection of tubercle bacilli.

Each column represents two months. In the tuberculous animals tubercle bacilli were injected at the end of two months and feeding was continued for four months following injection.

An examination of chart 1 shows that the cholesterol content of the plasma is similar to that of the whole blood. In the control animals following the injection of tubercle bacilli the cholesterol content continues to increase. The rabbit fed with oil and injected with tubercle bacilli

shows a decrease in cholesterol of the plasma, while the rabbit, fed with plain cotton-seed oil and not injected with tubercle bacilli, showed a slight continual rise in the cholesterol content.

The animals, which were fed with egg-yolk and cholesterol in cotton-seed oil and were not injected with tubercle bacilli, showed a continual and rapid increase in the cholesterol content of the plasma. The animals receiving similar feedings but injected with tubercle bacilli showed only a relatively slight increase in the cholesterol content of the plasma following the injection of the tubercle bacilli. It is possible that in these experiments, the results of which are similar to the experiments on whole blood, the injection of tubercle bacilli uses up in some possible way the free cholesterol and in this way retards or inhibits the further increase of the cholesterol content of the blood and plasma.

Cholesterol Esters: In the metabolism of cholesterol not all of the available cholesterol is taken up as such, and the ester of this compound, cholesterol ester, can still be determined by chemical methods, which differentiate the ester from the free cholesterol (Windaus, Knudson). We were interested in determining whether the cholesterol esters play any rôle in the further development or retardation of a tuberculous process. The experiments were similar to that described above, and, using the same sample of blood, cholesterol esters were determined by the method described by Bloor and Knudson. Examination of table 1 shows the amount of the esters in the whole blood and in the plasma. In some specimens of the normal rabbit blood and plasma the cholesterol esters were so small in amount that no readings could be obtained. However, after feeding, as well as after tubercle-bacilli injection, the cholesterol esters increased in amount. According to Bloor and Knudson the average percentage of cholesterol in the whole blood of the human being in combination as esters is about 33.5 per cent and in the plasma 58 per cent of the total cholesterol.

Fatty Acids: MacLeod states that normally the blood contains only a small percentage of fat, but after a fatty meal it may contain so large an amount that the fat actually rises to the surface of the blood like cream. After a fatty meal, absorption of fat takes place rather rapidly, so that the amount found in the blood may be increased in a relatively short time. When egg-yolk fat is fed, some of it may persist in the blood for several hours.

By examining table 1 it will be seen that the fatty acids in whole blood of the control animals, following the injection of tubercle bacilli, are less

than the average normal, but there is a return to the normal toward the end of the experiment. The animals, fed with plain cotton-seed oil, egg-yolk and the cholesterol in cotton-seed oil, showed a continuous increase in the fatty-acid content of the blood. Those animals receiving similar feedings but injected with tubercle bacilli showed a drop in the fatty acid of the blood (cotton-seed oil and tubercle bacilli) (no. 28), or there was an increase in the egg- and cholesterol-fed rabbits, but not so large in amount as in those rabbits which were not injected with tubercle bacilli.

The fatty acids in the plasma were almost similar in amount to that found in the whole blood, with the exception that in the control tuberculous rabbits (nos. 34 and 35) there was an increase after the tubercle-bacilli injection instead of a decrease, as was noted in the whole blood of the same animals.

By comparison of the fatty-acid and cholesterol contents of the blood during fat absorption, it has been found that there is a steady but variable increase in fatty acid, and accompanied by no variation in cholesterol. Iscovesco has noted that changes in cholesterol values generally do not come until late in the period of absorption. When small amounts of fat are being absorbed no changes at all may be noted in the cholesterol. Bloor is of the opinion that the increase of fat must reach a certain magnitude before lecithin is formed in notable amounts, and that lecithin must be similarly increased before cholesterol begins to increase. In persistent lipaemia both lecithin and cholesterol are increased along with the fat, the cholesterol to a greater extent than the lecithin. This observation has also been noted in our experiments, since the continuous feeding has simulated a condition of lipaemia. At the subsidence of the lipaemia, lecithin and cholesterol persist longest. A rather significant factor in fat metabolism is the difficulty to account for the increase in cholesterol, since a certain amount forms esters with fatty acids. However, the importance of cholesterol can possibly be sought for in its antagonistic action to lecithin, since this may exist in many of their relations in the living body. It may be that the increase of cholesterol following that of lecithin is a reaction whose purpose is to offset the injurious effects of an abnormally high concentration of lecithin. The significance of cholesterol in its action against tuberculosis, reasoning from the standpoint of empirical feeding of high-fat diets, will be discussed below. Chart 1 shows the lipoid ratios of the whole blood in the control and tuberculous animals.

Body Weights of Experimental Animals: As an index of recovery from a disease like tuberculosis, or a loss of weight indicating a progressive spread of the disease, clinicians have adopted the relative body weight as

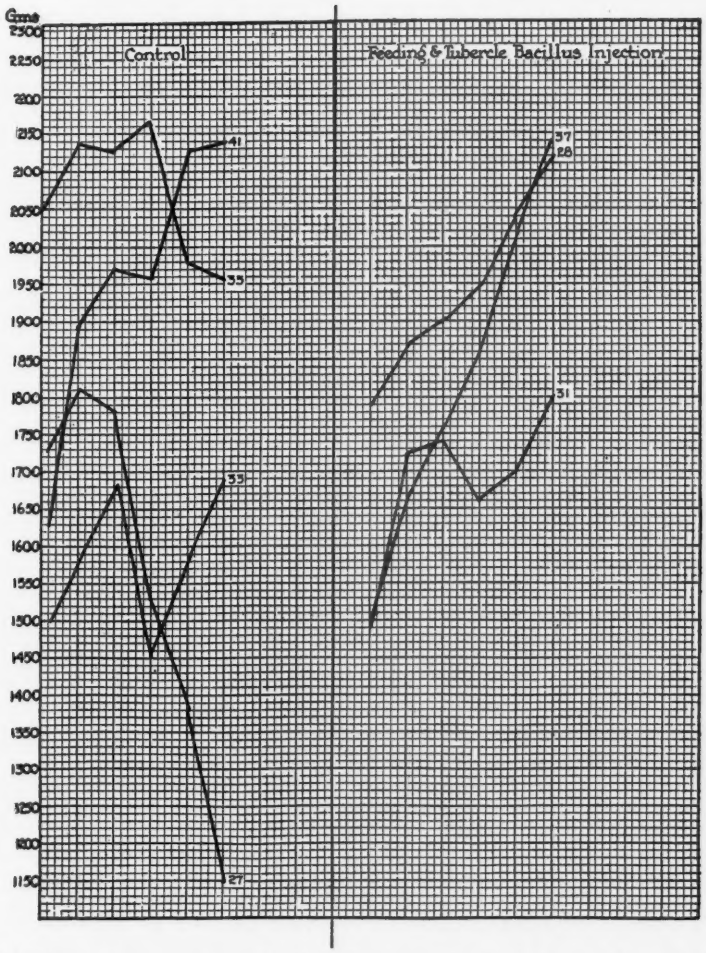

CHART 2. WEIGHT CURVES OF THE CONTROL TUBERCULOUS RABBITS AND CONTROL FEEDING RABBITS AS COMPARED WITH THE RABBITS INJECTED WITH TUBERCLE BACILLI
The numbers of the rabbits correspond with those rabbit numbers on chart 1

a standard of comparison. We were interested in the weight curves, as represented in chart 2, to determine the relationship this might have to the pathological findings observed at autopsy. As for the control tuberculous animals, in one (no. 35) there was a slight gain in weight and

then a drop to below its original weight; while in the other control rabbit (no. 34) there was a marked increase then a decrease, but at the end of the experiment the animal weighed more than its original weight. It is significant, however, that after the injection of tubercle bacilli there was always a slight gain in weight. The animal fed with plain cotton-seed oil and injected with tubercle bacilli showed a continuous increase in body weight, and the animal receiving the same feeding but not injected with tubercle bacilli showed first a slight increase and then a loss to below its original weight. The animal fed with egg-yolk increased in weight very rapidly, and the other animal, also fed with egg-yolk but injected with tubercle bacilli, showed a continuous and progressive increase in weight. The cholesterol-fed rabbit first showed an increase then a decrease to below its original weight and toward the end of the experiment there was an increase in body weight. The other animal fed with cholesterol but injected with tubercle bacilli showed a steady increase in body weight.

The above observations are significant, since in all these experiments it was noted that in those animals which were injected with tubercle bacilli there invariably was an increase in body weight. This fact indicates that in spite of the injection of tubercle bacilli there were no untoward ill effects on these animals, if we can attach any importance to the body weights. The animals receiving the various feedings lost in body weight, and this may be explained as being due to the extra burden placed upon these animals in the metabolism of the fats. However, similar feedings plus the injection of tubercle bacilli seemed to have the opposite effect, in that the animals showed an increase in their body weights. The control tuberculous animals also showed an increase in weight, and the explanation for this, as well as the above-mentioned observation, is problematical, since it was found that on autopsy there was a disseminated tuberculosis in nearly all the organs. The clinician has also observed that a progressive tuberculosis in human beings is associated with a loss in body weight.

Relative Proportion of Weight of Spleen to Adrenals: The importance of this phase of the question is in the rôle the adrenals play in fat metabolism, and in that of the spleen in the spread of tuberculosis. Webb and Ryder have indicated that the spleen can be used as an index of the spread of tuberculosis in tuberculous animals. We have, therefore, weighed the spleen of all the experimental animals, since the actual weight of this organ is a means of determining the amount of involvement

as well as attempting to find out the rôle in the defensive mechanism this may have against tuberculosis.

Recently Foote has shown that when the spleen is removed from rabbits the spread of tuberculosis in the body of these animals takes place at a more rapid rate than in those animals with the spleen intact. The explanation that the spleen contains enzymes that act in a defensive way against tuberculous infection has been propounded. The examination of

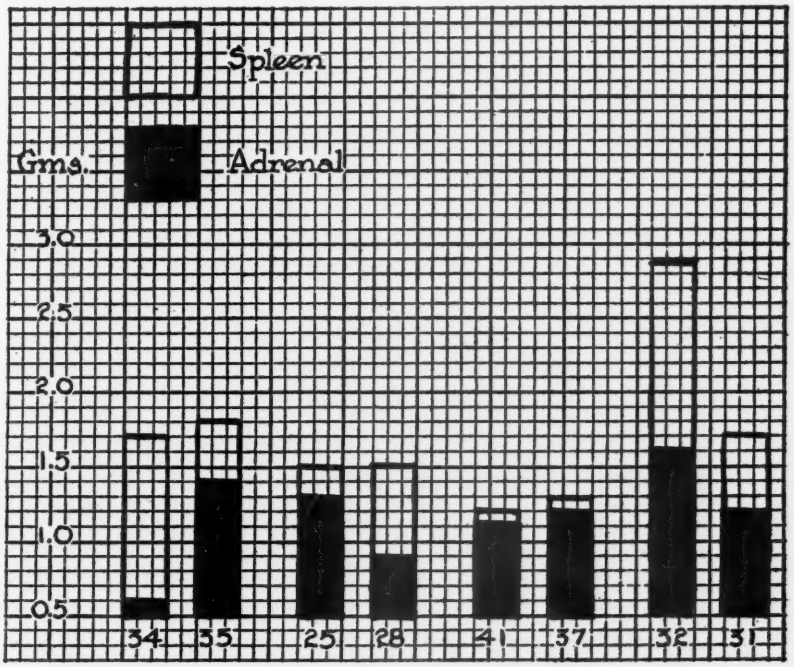

CHART 3. RELATIVE PROPORTIONS OF WEIGHTS OF SPLEEN TO ADRENALS IN THE CONTROL AND TUBERCULOUS ANIMALS

The numbers of the rabbits correspond with those on chart 1

chart 3 shows that in the control tuberculous animals the spleen was tremendously enlarged in one animal and in the other animal was within the normal range. In the rabbit fed with cotton-seed oil the spleen was smaller in size and weight, but in the animal receiving the same feeding and injected with tubercle bacilli the spleen was larger in size and the weight increased. In the animals fed with egg-yolk as well as those injected with tubercle bacilli the spleen was smaller and the weights decreased. The spleen was enlarged in the animal fed with cholesterol, but

in the tuberculous animal fed with cholesterol the spleen was not quite so enlarged as in the control cholesterol animal.

In the protocol the solid column represents the weight of the two adrenals. In the control tuberculous animals, in one rabbit the weight was small, and in the other rabbit there was quite an increase in weight. The adrenals of the cotton-seed-oil-fed rabbit weighed much more than in the rabbit which was also injected with tubercle bacilli. In fact in the control cotton-seed-oil-fed rabbit the adrenals weighed more than the liver. Similar feedings were observed in the egg-yolk-fed rabbits. The adrenals were 6 to 7 times the weight of the spleen. In the cholesterol-fed rabbits the adrenals were also tremendously enlarged as compared with the spleen.

Evidently the various feedings as well as the tubercle-bacilli injections seemed not to be injurious to the adrenals (Jaffé). On the contrary, if we can attach any significance to the weight of this organ there seems to be no difference as far as the gross pathology is concerned.

DISCUSSION

The literature on the subject of cholesterol and the rôle it plays in pathological reactions is so voluminous that we cannot attempt in this discussion to mention nearly all of it The references on the subject of cholesterol in tuberculosis are quite abundant, so that in the discussion of this paper we must confine ourselves to the subject as much as possible.

Of historical interest we might mention the work of Flint, who suggested that cholesterol is an important factor in intoxications, especially in icterus. He claimed that the liver excreted cholesterol from the blood and that any disturbance of this function, resulting in bile retention, caused an accumulation of cholesterol in the blood, with subsequent symptoms of toxaemia. Muller in 1873 and Pages in 1896 injected cholesterol into the blood-stream, with results which led them to confirm its toxic properties. An opposite view was taken by Felz and Ritter, who were of the opinion that cholesterol is nontoxic. Pauzer, Aschoff, as well as Smith and Dietrich, have devised methods for the differential staining of cholesterol esters. Morphological studies of cholesterol were made by Aschoff and a monograph on this subject was written by Kawamura.

Lander is of the opinion that the organism is capable of picking out and conserving cholesterol from a diet of exceedingly low cholesterol content. It is also generally believed that deposits of cholesterol esters occur pathologically at the sites of low-grade chronic inflammation, while

deposits of cholesterol crystals occur under conditions of slow cell destruction in areas where absorption is poor.

Beneficial effects were observed from the use of cholesterol, and Tunnicliff, in studying the effect of cholesterol in neutralizing the depressing effect of diphtheria toxin on phagocytosis, was able to demonstrate that cholesterol and diphtheria antitoxin are effective, normal horse-serum having no such influence. She also observed that the intravenous injection of a small dose of cholesterol into rabbits has a stimulating effect on phagocytosis, while a larger dose may have a depressing influence.

Luden records a series of experiments on herself, to observe the relation and reciprocal action between the diet, the blood cholesterol, and the lymphatic reaction or lymphoid defense. She is of the opinion that a diet which increases the blood cholesterol coincidently weakens the lymphoid defense. A diet which reduces the blood cholesterol coincidently increases the lymphoid defense. These findings do not seem to agree with the observations noticed with the empirical treatment of fats to increase the cholesterol content in order to increase bodily defensive factors. From our studies we are of the opinion that the animals in which a hypercholesterolaemia was produced did not seem to have the course of their tuberculosis favorably influenced.

It is of interest to note that, in some of the blood-chemistry studies made in relationship to tuberculosis, some investigators are of the opinion that cholesterol decreases in proportion to the severity of the disease and is of definite prognostic aid (Sweany, Petersen). This seems to be contrary to the view of Luden, who has found that high cholesterol values weaken lymphatic defense.

In recent years considerable work has been done along the lines of hypercholesterolaemia and its relationship to various diseases. K. Dewey has carried on an extensive experimental work on hypercholesterolaemia, and is of the opinion that the effects of the latter vary, not only according to the kind, size and number of the doses, but also greatly according to the general condition of the rabbit, individually, as well as physiologically and pathologically. The amount of cholesterol seems less essential than the degree of constitutional integrity and functional activity of the cell which prevails prior to the injection, or which results from the first establishment of an experimental hypercholesterolaemia. This observation of Dewey is in many ways similar to ours, since our histopathological studies of the various organs seem to emphasize the importance of them all toward infection. Similarly the weights of these

animals also indicate that feeding or overfeeding is not necessarily essential in the beneficial outcome of tuberculous infection, since according to Dewey the effect of hypercholesterolaemia depends to a certain extent on the general condition of the animal.

Attempts, however, have been made by numerous investigators to determine, if possible, the effect that cholesterol feeding has on various types of infection. Different methods have been used to introduce cholesterol into the system. Dewey injected a cholesterol emulsion intravenously into rabbits, while Sano has fed dogs on various diets and determined cholesterol and its compounds in the lymph from the thoracic duct. Versé has observed that, when rabbits are fed with cholesterol, absorption takes place very slowly and this leads to a gradual increase toward hypercholesterolaemia. This becomes more significant since Versé has shown that, within one month's time, the serum contains such a large amount of lipoid that this becomes visible to the naked eye. At the same time there is developed an arteriosclerosis of the aorta and other vessels (Anitschkow, Wacker and Hueck). Anitschkow, in experimenting with cats, rats and rabbits, fed these animals with a 4 per cent solution of cholesterin in sunflower oil, in amounts up to 30 cc. Fat infiltration with cholesterin esters was evident in the liver, the endothelial apparatus, suprarenal cortex and the walls of the arteries after a month or so of this alimentary hypercholesterolaemia.

Recently Schonheimer has demonstrated that, when sodium desoxycholate is added to fat in one feeding to rabbits or guinea-pigs, one can usually observe a lipaemia. The addition of desoxycholic acid to a fat diet containing cholesterin results in an increase of the cholesterol content of the rabbit much greater than without the addition of this acid. Desoxycholic acid alone does not increase the cholesterol content of the blood.

Analyzing the results of our experiments, we have shown that in feeding egg-yolk, which has a high cholesterol content (Wesselkin), and cholesterol in oil to rabbits, absorption takes place from the alimentary canal with relative rapidity, to increase the cholesterol level of the blood. Similarly Stepp, as well as Rosenthal and Holtzer, have also noticed the absorption of cholesterol from the alimentary tract into the blood-stream. It would be folly for one to attempt to judge the beneficial results obtained from this method of feeding, placing their opinion on the chemical studies alone without the knowledge of the pathological changes in the animal's body. The cholesterol content did increase in the blood and

plasma in the control-fed animals as well as in those which were also injected with tubercle bacilli, the increase being greater in the control-fed animals. The decrease in the cholesterol content of the blood and plasma, following the injection of tubercle bacilli, may be due to the organisms having used up the cholesterol, or to the cells in the body having utilized the cholesterol in building up a defense to ward off the spread of infection. But, when we compare the gross pathological findings in the animals fed with cholesterol and egg and those also injected with tubercle bacilli, the results were more favorable as far as the animals were concerned with the latter than with the former. This has been further corroborated by the histopathological findings reported elsewhere. Henning appears to be of the same opinion as ourselves in that he states that the reason for the apparent substitution for cholesterol in tuberculous blood is at present a matter of speculation; but, when the lipoid nature of the tubercle bacillus and of the tubercles is concerned, it seems reasonable to suspect that cholesterol may be involved in some way in the attempt of the body to protect itself from this microörganism. Hinze examined 69 patients with pulmonary tuberculosis, and showed that in the acute form of the disease the blood cholesterol is always low. He concludes that, the greater the cholesterol content of the blood, the greater the resistance of the patient to tuberculosis. Shope suggested the possibility of the use of cholesterol as a chemotherapeutic agent. Because the cholesterol can penetrate and localize in tubercles this investigator suggested combining cholesterol with radicals known to possess bactericidal properties. Using various compounds combined with cholesterol, Shope concludes that intraperitoneal injections in guinea pigs did not prolong the lives of these animals if the tubercle bacilli injected were of low virulence and large dosage, or if the tuberculous infection was of the chronic type produced by small doses of human tubercle bacilli of low virulence. However, these injections definitely prolonged the lives of guinea pigs when the infection was of an acute type produced by inoculating small doses of a very virulent microorganism.

Petersen and Levinson, from an examination of 83 tuberculous patients in various stages of the disease, are of the opinion that the cases of healed tuberculosis are usually associated with high cholesterol values.

Bloor and Knudson are of the opinion that, from a study of the lipoids in diabetic lipaemia, the inference seemed justified that cholesterol takes an important part in fat metabolism. The most obvious way in which

it would participate in fat metabolism is by its fatty-acid esters, which are always present in the blood and in most tissues, so that a knowledge of the balance between cholesterol and its esters in the blood would be of great value in the study of this function. Such knowledge would also be of value in the study of other functions of cholesterol, as, for example, the part which it plays as an antihaemolytic (Ransom), when the protective power depends on the amount of free cholesterol present. The weight-curves seem important, since invariably the animals which were on the various diets and which were not injected with tubercle bacilli lost weight, while the animals injected with tubercle bacilli as well as those also fed with egg-yolk and cholesterol gained weight.

CONCLUSIONS

1. Feeding egg-yolk and cholesterol in oil to rabbits gives rise to a relatively rapid increase of the cholesterol level of the blood.

2. Cotton-seed-oil feeding is not injurious to the mucosa of the gastro-intestinal tract.

3. A gain in weight was noted in those animals which were injected with tubercle bacilli and which received the various fat feedings. The animals fed with oil and not injected with tubercle bacilli usually showed a loss in weight.

4. Overfeeding with cholesterol, leading to oversaturation of the body of the rabbit with cholesterol, does not protect the animal against tuberculosis.

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THE DIETARY TREATMENT OF TUBERCULOSIS

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Since the establishment of the first sanatorium by Brehmer, the importance of adequate feeding as an essential part of the treatment of tuberculosis has been emphasized by all those closely connected with the management of this disease. Still statistical data from many American sanatoria, a survey of the sanatorium diet in Germany by Schroeder and Kaufmann (1), and a recent analysis of the answers of 36 well-known phthisiologists to his questionnaire by Hawes (2), reveal widely divergent views as regards the diet in pulmonary tuberculosis. Nevertheless there is unmistakable evidence of a tendency to change from a purely empirical, to a rationalized, from an ultraliberal overfeeding to a diet adapted in its quantity and composition to the requirements of the diseased body. Clinical experience, laboratory observations, and experimental studies on animals teach us that the pathological changes with their varied clinical manifestations, resulting from infection by tubercle bacilli, should form the only basis for building up a set of dietetic rules for our patients. The scientific knowledge of the effect of diet on tuberculosis has developed within the last fifteen or twenty years. Previous to that a good deal was known in regard to the chemistry and digestion of foods. Even to-day the gap between theoretical considerations, experimental results and practical applicability of new principles concerning diet in tuberculosis needs to be overbridged.

The diet introduced by Sauerbruch, Hermannsdorfer and Gerson (3) was construed to establish a shifting of the acid-base balance toward the acid side, the depletion of the water contents of body tissues, shifting in the ion contents of the body by substitution of the sodium by calcium, and remineralization.

On the average 3,000 calories are given daily; approximately 45–50 calories per kg. of body weight; the proportion of protein, fat and carbohydrate being P:F:C = 1.5:2.7:3.7. The diet card of a patient presents the following appearance:

[1] Muirdale Sanatorium, Wauwatosa, Wisconsin.

Prohibited Foods

Table salt, canned goods of all kinds, smoked and spiced meats, sausage and ham, smoked or salted fish, vinegar, maggi, bouillon.

Foods Permitted in Restricted Quantities

Flour of all kinds, unsalted bread, whole rye bread, pumpernickel, zwieback, noodles, macaroni, pastry, fresh meat (500 gm. a week), sweetbread, brain, liver, lungs, kidneys, spleen, fresh fish, peppers, Liebig's meat extract, beer, malaga, red wine (along with meals), coffee, tea, cocoa, only enough to color the milk.

Permitted Foods

Milk: from 1 to 1.5 litres daily, in any form, especially raw milk; but also sour milk, milk cocoa, milk in puddings or rice, cream, salt-poor cheese, curds, unsalted dairy butter. Fruits of all kinds: large amount of raw fruit, but also stewed fruits, marmalade, jellies, fruit juices, apple cider, "fruit wines," fruit salad, baked apples. Fresh vegetables (which are to be steamed, the vegetable juices being retained) as follows: tomatoes, carrots, turnips, salsify, potatoes, kohlrabi, leeks, beets, asparagus, cauliflower, cabbage (red and white), savoy, cress, endive, lettuce, sorrel, spinach, peas, beans, lentils, mushrooms, cucumbers and melons. Raw carrots, rubbed in sugar, may be used; also the raw expressed juices of vegetables may be added to soups and other foods. Eggs; also in mayonnaise, puddings, broth, cake. Rice (unpolished Rangoon variety), wheat grits, cornstarch, tapioca, peeled grains, oatmeal. Sugar, especially brown sugar, and pure honey. Olive oil and lard.

Abundant and diversified use of the following seasonings or spices should be made, in order that the lack of table salt in the food may not be noticed: glace, bonemeal, allspice, marjoram, estragon, dill, borage, onions, peppermint, laurel leaves, chive, caraway, lemon, parsley, celery, garlic, horseradish, radish, pot herbs, ginger, vanilla, cinnamon, anise, dried currants, almonds, cocoanut, nuts, raisins, yeast.

The following is a typical dietary and diet schedule for one day:

7 A.M.: Heavy soup, milk 10 ounces, some water, oat flakes, rice, or farina, or tapioca, or similar preparations, one-half of one egg, tablespoonful of butter, some sugar, lemon, cinnamon, or vanilla.
9 A.M.: Thin coffee with much milk. Bread, butter, marmalade, or honey.
10 A. M.: Fruits for desserts.
12:30 P.M.: Dinner with fruit.
4 P.M.: Milk (cocoa or coffee), cake, zwieback, butter, or marmalade.
6:30 P.M.: Supper with fruits.
8 P.M.: Soup as in A.M.

Besides this diet the patients are given 45 gm. phosphorcodliver oil (phosphorus 0.025 gm., oleum jecoris 300 gm.) and *mineralogen*, one teaspoonful, t.i.d.p.c., in watery suspension.

It is interesting to note that since the last quarter of 1929 the use of phosphorcodliver oil was greatly restricted and partly substituted by *radiostol* (irradiated ergosterol) by Gerson (4). He prescribes one tablespoonful of phosphorcodliver oil, b.i.d., for three days alternating with three days on radiostol (one dragée b.i.d.) medication. Several observers, as Bergmann, Birk, Bacmeister, Plath, and Menschel (5), assume that the beneficial effect of this diet rests upon the action of vitamine D. Bergmann expressed the idea that, if rickets is curable by irradiated ergosterol as well as by heliotherapy, good therapeutic results may be expected from the same drug in tuberculosis, the orthopaedic and other extrapulmonary forms of which in general, and also selected types of pulmonary cases, are successfully treated by exposure to ultraviolet rays. The results of Menschel with *vigantol* (irradiated ergosterol) in tuberculosis were very good. Scheurlen and Orlowitsch-Wolk (6), on the other hand, were not able to corroborate Menschel's observations. Gerson (4) does not consider codliver oil or irradiated ergosterol as having primary importance in his diet. He reports cases of lupus, joint and pulmonary tuberculosis with remarkable improvement on salt-free diet, without the addition of codliver oil and points out the futile trials of the past to cure tuberculosis by codliver-oil medication. Similar opinion as to the effect of this preparation upon tuberculosis was expressed by Smith (7), who saw no change in the course of tuberculosis in guinea pigs following codliver-oil treatment.

Mineralogen consists of ten different salts, namely, calcium lactate, calcium phosphate, sodium sulphate, sodium silicate, potassium aluminum sulphate, sodium acid sulphate, sodium bromide, bismuth subnitrate, strontium lactate, magnesium sulphate, and contains also a small amount of albumin.

Gerson (3), whose empirical observations added the necessary momentum to an extensive scientific investigation of this new method of treatment in tuberculosis, started out with the theory that, by certain shifting in the mineral metabolism by variations in the diet, one may be able to influence many diseases. His results were rather encouraging in different nervous conditions and, incidentally, he noticed a rapid healing of tuberculous foci in his patients.

The study of the effect of this diet upon tuberculosis was based upon

the previous experience of Sauerbruch in treating wounds. He (8) describes a case of perinephritic and liver abscess which, in spite of wide surgical opening, perforated into the pleural cavity, producing a pyogenic empyema with febrile temperature, loss of weight and consistent weakening of the patient, despite the forced feeding instituted. When, however, the patient refused to take any more nourishment, after a few days' fasting a remarkably rapid healing of the empyema and of the operative wound and a complete recovery of the patient followed. According to his opinion, hunger acidosis should be considered as the cause of healing in this case. A somewhat similar observation is reported by Kalk (9) on a patient, who, due to repeatedly prolonged roentgen-ray exposures, developed an ulcer on his back, 23 cm. by 11 cm. in size, which persisted unchanged despite every possible medical care for fifteen years. Then the patient developed cancer of the oesophagus with marked stenosis, amounting practically to complete obstruction, so that he was unable to take any food. During the following eight-day observation period the wound started to heal spontaneously, the secretion diminished, granulation filled in the whole ulcerated area, which became perfectly epithelialized, with the exception of a comparatively small area, when the patient died. Kalk (9) quotes Stickler and Siegert, who state that infants with pyloric stenosis do not contract infections as easily as normal babies. Acidosis has been supposed to be the chief cause of tissue reaction against infectious microörganisms in their cases.

Clairmont (10) reports a case of infected nephrolithiasis, in which a pyelotomy was performed without any improvement in the patient's general or local condition until medication of hydrochloric acid was instituted, when a surprisingly rapid improvement and healing ensued. He claims that a favorable influence can be exerted upon pathological conditions caused by staphylococcus or colon-bacillus infection by this measure. Less favorable results were observed by him in streptococcus infections.

The observations of Sauerbruch with regard to the effect of the *S. H. G.* (Sauerbruch, Hermannsdorfer, Gerson) diet upon wounds in general can be summarized in the following points: (1) decrease of secretion; (2) shrinkage and better organization of the granulation tissue; (3) loss of odor; (4) decrease in the number of bacteria; (5) lessened viability and virulence of the bacteria; and (6) the microörganisms isolated from the wound have a tendency to become gram-negative. The findings of Hermannsdorfer (11) in his experimental and clinical investigations are

in harmony with the above observations. He found that the skin wounds of guinea pigs fed on oats and phosphoric acid showed a good tendency to granulation, contraction and healing, while guinea pigs fed on sodium bicarbonate and green vegetables presented a torpid wound without healing tendency. He states that an acid diet (acid chemically and not according to its taste), composed of meat, eggs, fish, butter, lard, cheese, flour, oatmeal, rice, cornmeal bread, lentils, nuts, cocoa, meat extracts, and beer, will effect a decrease of the alkali reserve of the blood and an increase of the hydrogen-ion concentration of the tissues. These changes can be enhanced by the addition of 25 cc. of a 25 per cent solution of phosphoric acid daily to the diet. On such medication the wound secretion becomes less, microörganisms disappear and the granulation surface contracts. The most favorable results were seen in proteus and pyocyaneus infections, while a less satisfactory response was found in conditions caused by streptococci and staphylococci. According to Sauerbruch (8), the local acidosis of the tissues and the lowering of the alkali reserve of the blood in diseases with suppurative wounds should be considered as a defense manifestation of the body and not as a by-product of the inflammatory process. Alkalinization of the body, by means of a vegetable and fruit diet and by the addition of 20 gm. of sodium bicarbonate daily, will be followed by increased wound secretion, an increase in the oedema of the surrounding tissues, grayish deposits on the granulation tissue, disintegration of the newly formed epithelium, an increase of the number of the microörganisms and a tendency of the bacteria to become gram-positive.

Bardenhauer (12) applied the Sauerbruch, Hermannsdorfer, Gerson diet in obstetrical cases, and reports that inflammatory processes, septic complications, deodorization of the puerperal fluor, the postpartum involution of the uterus and a normal course of the puerperium can be more successfully influenced and their treatment more effectively accomplished on this diet than on the regular diet.

Lately a definite divergence crystallized out between the diet given by Sauerbruch and Hermannsdorfer and that of Gerson. Gerson (13) decreased the amount of proteins to 67 gm. per day, the only exceptions to this being patients with anorexia, intestinal disturbances and malaise. In such cases he allows additional protein, three to four times a week. Hermannsdorfer gives 100 gm. of proteins daily. The amount of milk was reduced by Gerson from the original 1–1.5 litre daily to 250 gm. Furthermore, all fluid intake, in the form of coffee, tea, water, soda water

and soup, is forbidden, and the water intake is taken care of by the ingestion of 1400 gm. of vegetable juice and 600 gm. of fruit juice. The high vitamine and mineral-salt contents, as valuable constituents of vegetable juices, are emphasized in his later studies. His list of prohibited foods includes alcohol in any form, cocoa, chocolate, white bread, rolls and cream,—the latter except when it is used for preparing other dishes. The weekly amount of sugar and honey is reduced to 20 and 50 gm. respectively. The daily intake of 200 gm. of liquids is an evident contradiction to the original dehydration theory. Gerson does not share the opinion that it is necessary to restrict the fluid intake in order to produce a desiccation of body tissues. He claims that satisfactory loss of water can be induced by salt-free diet alone. According to his last diet scheme the total daily salt intake should be from about 1.6 to 2.7 gm.

The following table, as given by Gerson, represents the new diet formula:

Daily	Milk	250 gm.	400 mgm. NaCl. content
	Cream	10 gm.	15 mgm. NaCl. content
	Cheese	20 gm.	40 mgm. NaCl. content
	Sweet butter	100 gm.	30 mgm. NaCl. content
	Gerson bread	60 gm.	6 mgm. NaCl. content
	Potatoes	300 gm.	150 mgm. NaCl. content
	Oatmeal	40 gm.	60 mgm. NaCl. content
	Oil	25 gm.	
	Vegetables	500 gm.	550 mgm. NaCl. content
	Fruit	500 gm.	150 mgm. NaCl. content
	Egg yolks	4	32 mgm. NaCl. content
			1,433 mgm. NaCl. content
Weekly	Cream	150 gm.	195 mgm. NaCl. content
	Egg	1	35 mgm. NaCl. content
	Egg yolks	1	3 mgm. NaCl. content
	Sugar	20 gm.	20 mgm. NaCl. content
	Honey	50 gm.	
	Cream of wheat	50 gm.	3 mgm. NaCl. content
	Meat	100 gm.	130 mgm. NaCl. content
	Fish	70 gm.	66 mgm. NaCl. content
	Wheat flour	35 gm.	3 mgm. NaCl. content
	Rice	50 gm.	31 mgm. NaCl. content
	Almond	100 gm.	40 mgm. NaCl. content
	Nuts	100 gm.	110 mgm. NaCl. content
	Dried prunes	200 gm.	240 mgm. NaCl. content
			876:7=125 mgm. NaCl daily
			1,433
Total daily NaCl intake			1,558 mgm.

This composition represents 67 gm. of proteins = 275 calories, or 10 per cent of total daily caloric intake; 170 gm. of fats, equal to 1,581 calories, or 56 per cent of the daily caloric intake; and 235 gm. of carbohydrates = 964 calories, that is, 34 per cent of the total daily caloric intake, which is 2,820 calories.

Severe acidosis may occur in the terminal stages of many diseases due to accumulation of acids from increased metabolism and impaired cell function. The decrease of alkali reserve in such cases usually parallels the clinical condition, changing to the worse. Under normal circumstances the reaction of the blood and tissues is remarkably uniform and constant, in spite of metabolic changes producing and adding acid to them, due to the presence of buffers in the blood and in the tissues and to the prompt and exact regulating excretory effect of the kidneys and lungs.

A decrease in the alkali reserve of the blood in far-advanced, febrile, toxic pulmonary tuberculosis cases was found by Hachen (14). Sweany (15) was unable to detect an abnormally low alkali reserve or a true acidosis as a result of tuberculosis in his recent extensive clinical studies. The average alkali reserve in tuberculosis was found to be slightly below the average of healthy individuals though still within normal limits. Yet it is interesting to note that fibroid cases had a higher average of alkali reserve than exudative or rapidly progressive forms.

The standpoint of Sauerbruch with regard to the favorable effect of acidosis and acid diet upon wounds is diametrically opposed by the reports of Balint and his co-workers (16), supported by clinical and experimental investigations. They found an increased acid reaction of the blood and tissues in gastric-ulcer cases, and proposed to consider this increased acidity as the cause of gastric-ulcer formation. Balint thinks that the origin of varicose ulcers must be sought in the increased acidity of the tissues resulting from the stagnation of blood in such cases. In their experiments gastric and skin ulcers showed better healing in animals with increased alkali intake than in control animals, while increased acid intake retarded the healing process.

The most important feature of the S. H. G. diet is the decreased sodium chloride and increased calcium intake, which aims, first, to increase the acidity of the tissues; second, to supply the necessary amount of calcium to the blood and maintain a positive calcium metabolism; and, third, to promote healing and calcification of tuberculous lesions. That substitution of one ion by another can be successfully accomplished is

proved by the enhancement of the effect of sodium-bromide medication in epilepsy, while sodium-chloride intake is restricted. Sauerbruch maintains that shifting of the tissue reaction toward acid will induce leucocytosis, improve phagocytosis, and change the dissociation of calcium and potassium ions. According to Bunge (17) sodium-chloride inanition can be produced by vegetable diet. He states, furthermore, that normal sodium-chloride balance can be maintained in the average person on 2 gm. of table salt *per diem*; and that the difference between this amount and the usual daily intake of from 15 to 18 gm. should be considered as condiment, which can be eliminated or replaced without any harm to the body. In case of restricted sodium-chloride intake, the normal osmotic pressure will be preserved by a decreased renal excretion of salt. Sapiro (18) was able to prove that calcium may cause an increased acidity and noticeable depletion of the water content of the tissues. Luithlen (19) found that the skin of experimental animals fed on oats became rich in potassium and poor in calcium, magnesium and sodium; feeding on green vegetables produced an increase of all bases, especially calcium and magnesium. He demonstrated a decreased potassium and sodium and an increased calcium and magnesium content of the skin in animals on acid feeding, and an increased excretion of sodium, potassium and magnesium ions by calcium medication. Stolpe and Dubois (20) showed that a vegetable diet rich in potassium will increase the retention of calcium.

The sodium-chloride content of the blood is usually high in febrile diseases, such as typhoid fever, scarlet fever, pneumonia, erysipelas, and in conditions with oedema or inflammatory exudation. It is, therefore, rather against expectation to note that hypochloraemia was found in tuberculosis by several investigators (21). Meyerowitsch (22) investigated the sodium-chloride metabolism in tuberculosis, and reports that the sodium-chloride balance in these cases is subject to the same laws that govern it in other inflammatory conditions; salt retention was observed with rising temperature, large exudate formation and oedema, and an increased salt excretion with the remission of fever.

The administration of mineralogen in connection with the S. H. G. diet is based also upon the thesis first championed by Robin and Binet (23). According to their studies, demineralization, that is, a loss of mineral substances from the body, should be considered a characteristic feature of tuberculosis. They found an increased excretion of calcium and magnesium salts through the kidneys in tuberculosis and pretuber-

culosis cases. As the result of this abnormal elimination of mineral substances a depletion of calcium and magnesium contents of the blood, lungs, bones, liver, kidneys and muscles was noted. Furthermore, they reported decreased ash values in tuberculous lungs, and increased ash values in healthy portions of the lungs. Basing their conception upon these findings, they maintained that the normal mineral content of the tissues is indispensable for the normal resistance and defense mechanism of the body against tubercle bacilli. The demineralization theory was supported by vonNoorden (24) and other tuberculosis workers; still, the problem does not seem to be settled. Ott (25) found retention of minerals in tuberculosis cases with positive nitrogen balance and a loss of mineral substances in cases in which a negative nitrogen balance was seen. His investigations revealed that the mineral metabolism is normal in early forms. He states that an increased mineral excretion which may occur in advanced cases is due to fever and undernutrition and not to tuberculosis itself. Winternitz (26) does not consider the loss of minerals as a characteristic phenomenon in tuberculosis. Wells (27) says that "despite the widespread belief that tuberculosis is characterized by a marked loss of inorganic elements, there is no evidence for such a process in carefully controlled observations on mineral metabolism. At most, the losses of salts are no greater in tuberculosis than in other conditions with a corresponding loss of weight."

Particular interest has been focused in the study of mineral metabolism in tuberculosis upon the behavior of calcium because of the frequent presence of calcium salts in healed tuberculous lesions. With regard to the use of calcium in the diet or as an addition to the diet two questions arise: first, is it possible to increase the calcium content of the blood and tissues by calcium medication; and, second, does an increase in the calcium content of the blood exert any favorable effect upon the course of tuberculosis? The amount of calcium in the total blood of a man of 60-kg. (135 lbs.) weight is approximately 0.5 gm.; the bones contain about 4000 times as much, serving as a reservoir for the preservation of the normal calcium level. It has been proved in the treatment of rickets, tetany and osteomalacia that the blood calcium can be effectively raised by appropriate diet and medication. Beneficial results have been reported in premature infants, bone fractures and dental caries by the use of irradiated ergosterol, by which it is possible not only to restore a low calcium level to normal but also to induce hypercalcaemia. The question of calcium deficiency in tuberculosis seems to be just as con-

troversial as that of the mineral metabolism in general. A great many observers, as Steinitz and Weigert, Labbe and Gallipe, Vannini, Mayer, and Muggia (28) have found no loss of calcium, corroborating the findings of those opposing the theory of demineralization. Barkus (29) was unable to detect an appreciable loss of calcium in tissues of tuberculous guinea pigs. Reduced calcium content of the blood was observed by Sweany, Weathers and McCluskey (30) in pulmonary-haemorrhage cases. McCann (31) states that more calcium is necessary for the calcium balance in tuberculosis than under normal circumstances.

The normal adult requirement of calcium *per diem* is estimated from 0.33 to 1.43 gm. of calcium oxide. The manifold pharmacodynamic effect of this element is well known. Calcium decreases the irritability of striated muscles, aids coagulation, diminishes inflammatory exudation, stimulates the sympathetic nervous system, increases blood-pressure, aids immunological response and modifies the anaphylactic manifestations of the body. Many clinicians reported favorable results from the use of calcium salts in the treatment of tuberculosis. The findings with regard to the absorption and utilization of calcium are quite divergent. Bogert and Kirkpatrick (32) were able to demonstrate that acid-forming foods improve, while base-forming foods retard calcium absorption and retention. Sato (33) saw an unfavorable effect of alkali upon calcium metabolism. Orr, Holt, Wilkins and Boone (34) maintain that an increased acidity of the intestinal contents and an increase of the total salt concentration will aid the absorption of calcium. Meigs, Blatherwick and Cary (35) showed that the blood calcium can be increased by calcium-lactate medication in cattle, and that there is an antagonism between calcium and phosphorus as far as their intestinal absorption is concerned. This latter observation was corroborated by Schabad (36) in children. Bosworth and Bowditch (37) found an increased calcium retention and loss of phosphorus in children on calcium-chloride medication. Denis (38) did not find an increased blood calcium in persons given calcium lactate orally. On the other hand, Voorhove (39) and Towles (40) claim to have found retention of calcium when food containing large amounts of calcium was fed. Matz (41) concludes from his studies that "the ingestion of inorganic calcium salts, both in normal and tuberculous subjects, resulted in a rise of the calcium concentration of the blood. The rise following the use of calcium chloride was greater, and extended over a longer period than after the ingestion of calcium lactate." Kost (42) found an increase of the

calcium content of the tissues of animals fed on calcium, and Tanaka (43) was able to induce metastatic deposition of calcium after intravenous injection of lime salts. The results of the experiments of Maver and Wells (44) with regard to the favorable influence of calcium medication upon the course of tuberculosis were entirely negative. Wersen (45) observed calcification of the tracheobronchial lymph nodes in a larger number of children given calcium lactate orally than in the untreated controls.

The advocates of the remineralization therapy claim that it is possible to increase the calcium content of the blood by calcium medication, and that by means of an increased blood calcium it is possible to induce calcification of tuberculous lesions.

The first report of Sauerbruch, Hermannsdorfer and Gerson concerning their special diet in tuberculosis describes their results in 43 pulmonary, 20 bone and joint, and 8 skin tuberculosis cases. The length of treatment varied from three to nine months. The first manifestations of improvement, such as gain in weight, decrease of temperature and pulse-rate, gain in strength and better general appearance, were observed after several weeks of treatment, though transitional relapses did occur. In pulmonary cases they saw a change of sputum from purulent into mucopurulent, and a diminution of the amount of and a lessening of the number of tubercle bacilli in the sputum. Out of the 43 pulmonary cases, 11 were not analyzed because the observation period was less than a month, six showed marked improvement, 10 improved, 15 remained unimproved, and one died. Out of the 20 bone and joint cases eight were not analyzed for the same reason as above, three presented marked and seven moderate improvement, two remained unimproved. Marked improvement was found in six, and moderate improvement in one case of skin tuberculosis. Both in orthopaedic and in lupus cases an occasional inflammatory reaction was seen shortly after the beginning of the treatment. Very favorable results were reported in pulmonary tuberculosis by Clairmont. He found that patients under this treatment stand operation better and that the postoperative improvement of the local and constitutional symptoms and signs is more rapid than usual. Further favorable reports were published by Sauerbruch and Hermannsdorfer (46) in 1928, and by Baer, Hermannsdorfer and Kausch (47) in 1929. The length of observation of cases reported in detail varied from five to fourteen months, and the gain in weight from 6.5 to 27 kg. (14.6 — 56.2 lbs.). They emphasize the fact that many

of their patients have been under institutional treatment without improvement and showed amelioration on the S. H. G. diet only. Some patients gained in weight from the first week on; others suffered a slight loss of weight during the first few weeks with rapid gain subsequently. Remission of the temperature or its return to normal, a decrease or disappearance of cough and expectoration, a cessation of night-sweats and lessening of complaints in general were recorded in many cases as early as the first and second months. They found clinical and roentgenological evidence of the transformation of an exudative process into a fibrotic one. According to their experience, in some bilateral cases one side may be brought to healing by this diet and the patient rendered operable; its postoperative use may prevent the spread of the disease to the opposite side. They suggest the institution of this diet in all cases of tuberculosis in which the resistance and defense mechanism of the body are low.

The original work of Sauerbruch, Hermannsdorfer and Gerson was followed up by studies of many investigators, some of them being quite enthusiastic about it, while others are rather skeptical as to its usefulness. Mueller-Scheven, Ritschel, Wiegand, Guttkant, Schwalm, Liesenfeld, VanderReis, Harms and Gruenewald (48) found no more improvement on the S. H. G. than on regular sanatorium diet. The results of Apitz (49) in orthopaedic tuberculosis of children were not better than under routine care, while good therapeutic effect was seen in the same type of cases by Strausz (50). Westfahl (51) saw some increase in weight without improvement in the physical findings. Pfeffer (52) was not able to find any change in the hydrogen-ion concentration of the blood in patients on this diet. Out of 40 patients observed by Pfeffer one showed marked, 16 moderate improvement, seven remained unchanged, and 16 presented changes for the worse. Bettmann (53) states that the diet must have been discontinued because of loss of appetite in the majority of his cases. Increase in weight and abatement of constitutional symptoms were noted by Kretz (51); however, he could not find a direct influence of the S. H. G. diet upon the course of the pulmonary process.

The results obtained in his 50 cases can be summarized as follows: Out of 30 patients with bilateral tuberculosis of the lungs 22 were unimproved (out of this number 16 died), and eight improved; four unimproved and ten improved cases were found among 14 with unilateral lesion complicated by cavitation; two unimproved and four improved cases occurred among six patients with fibrous apical processes. Due to the loss of appetite seen in his cases, which he attributes to the lack of

salt from the diet, Kretz suggests a diet poor in salts instead of the salt-free diet.

Favorable results were reported by Steiner and by Brugsch (54). Alexander (55) obtained undoubtedly good effects from this diet in some of his cases; still, he maintains that no improvement can be established under this regimen in far-advanced pulmonary tuberculosis. Remarkably good results have been reported in the treatment of lupus vulgaris by Jesionek (56). He, however, expressed the opinion that mineralogen, in addition to the regular diet, has no influence upon lupus; furthermore, that a salt-free diet may give just as good results without mineralogen as with it; and that the exclusion of mineralogen from the diet of patients who were taking it before does not cause any change in the healing of lupus as long as patients were given salt-free diet. The effect of the S. H. G. diet upon radiodermatitis, hypertrophic scars and lupus was studied by Brommer and Bernhard (57). They stated that dietotherapy in connection with general therapeutic measures should be considered as the most efficient single procedure in the treatment of lupus vulgaris. They claim that it surpasses every other method of treatment in its cosmetic results. According to their observation favorable changes can be seen as soon as a few days after the institution of this diet. The bluish-red discoloration around the yellowish-brown lupus nodules will fade away and change into a light yellow color; the oedema surrounding the nodules disappears; later on the nodules become smaller, the light red halo around the nodules clears up, and the previously infiltrated areas heal without scar-formation or with small, hardly visible scars. Similar favorable results have been described by them in lupus of the mucous membranes of the mouth, nose, throat and larynx. The rapidity of healing may be greatly increased by the combined use of the S. H. G. diet and ultraviolet irradiation. The only work in the American literature that we had access to is the study of Mayer and Kugelmass (58). From the analysis of their 20 cases they note the disappearance of fatigue and thoracic pains in general, and that eight patients gained considerably in weight, ten showed marked diminution of sputum, and four became afebrile; in eight definite clearing was demonstrable on physical and roentgen-ray examination, and in two symptoms of intestinal tuberculosis cleared up. In a recent report, based on the analysis of 300 cases, Hermannsdorfer (59) brings out additional evidence as to the value of this diet in the treatment of tuberculosis.

Our study was started in September, 1929, after thorough investigation

of the available information concerning this subject. Certain technical difficulties arising from the arrangement of such a diet in any institution, no matter how well and modernly equipped it is as far as culinary requirements are concerned, are inevitable, and should be taken into consideration when planning this regimen. The merits of the dietitian taking care of the exact and tasteful preparation of salt-free dishes must not be underestimated. It must be kept in mind that, in patients given this diet, we are dealing with cases with marked toxic symptoms and usually a poor appetite. The utmost care and knowledge and real art of dietetics are necessary to overcome obstacles arising from this situation and to enable us to ensure a qualitatively and quantitatively adequate intake of nourishment for our patients. These surely will help us to counteract undue passive resistance and lack of coöperation on the part of the patient. We had the opportunity to experience that in more than one of our cases. It would be ideal to serve all salt-free meals in a separate dining-room. In our cases, mostly strict bed patients having been included in this analysis, it was comparatively easy to make serving arrangements.

Our study may be separated into three different periods. During the first period, the 24-hour dietary was prepared exactly as advised by Sauerbruch, Hermannsdorfer and Gerson, giving 90 gm. of proteins, 162 gm. of fats and 222 gm. of carbohydrates. In the second period the caloric intake was slightly increased, approaching our standard diet yet following the prescribed proportion of proteins, fats, and carbohydrates, P:F:C = 1.5:2.7:3.7. In the third period we slightly increased the fat and decreased the carbohydrate intake. In planning this form of diet two points were suggestive: first, favorable reports on the effects of fats upon the course of tuberculosis, and, second, the metabolic behavior of fats and carbohydrates in their relation to tuberculosis. Weigert (60) found that animals overfed on fat showed an increased and animals fed on carbohydrates a lessened resistance against tuberculous infection. These findings were corroborated by Vogt (61) in children. He found that children fed on food rich in fat presented a higher resistance against tuberculous infection than normal controls fed on customary diets. The concrete analytical studies of McCann (62) contribute additional proof of the rationale of a diet rich in fat for the treatment of tuberculosis. That febrile temperature involves an increase in the metabolic rate is well known. Several observers found an increase in the metabolic rate of from 15 to 35 per cent in patients with afebrile, severe types of

tuberculous pulmonary lesion. In a series of 50 cases studied at this institution we found a supernormal metabolic rate in 42 per cent. The increased metabolism will increase the oxygen intake and the carbon-dioxide production. Carbon dioxide, being a respiratory stimulant, will augment the respiratory function, first, by its direct stimulating effect, and, second, because an increased respiratory function is necessary for the elimination of the abnormally large amounts of carbon dioxide. At the same time the vital capacity is decreased, due to the diminished respiratory surface caused by the tuberculous involvement of the parenchyma, eventual sclerosis, pleural adhesions, and reflex respiratory inhibition. When, therefore, all our therapeutic efforts in the treatment of pulmonary tuberculosis aim at the maximum rest for the involved lungs, it is evident that McCann's suggestion, that the diet in these cases ought to be construed to throw as little demand as possible upon the anatomically damaged and functionally incompetent cardiorespiratory system, should be considered as a valuable contribution to the scientific management of tuberculosis. He states that for one unit of heat produced from glucose there is a production of nearly 30 per cent more of carbon dioxide than with the same energy production from fat. He maintains that, if the patient tolerates fats well, a diet may be given which involves very little increase in the respiratory function, and that "satisfactory nutrition may be attained by the use of moderate quantities of proteins (60 — 90 gm. *per diem*), with fats up to the limits of digestive capacity, and sufficient carbohydrates to bring the total caloric value to from 2500 to 3000 calories. Such a diet will produce the least demand upon the function of the damaged lungs."

The food was served in three meals. In our mind it did not seem practical to overtax the patient's digestive system with seven servings a day, as practised by German clinicians. No table salt was added to the food. Calcium appeared to be the main constituent of mineralogen; therefore, we resorted to the administration of calcium chloride or calcium lactate, of each of these gr. 15, t.i.d.p.c., and later on 75 grains daily were given throughout the course of the diet. Some of our patients showed very poor tolerance to calcium; vomiting after medication was occasionally observed, more often due to calcium chloride than to calcium lactate. In a case of renal tuberculosis the calcium administration had to be discontinued because of marked frequency and dysuria. Kretz suggested the use of the following mixture instead of mineralogen:

	grams
Sodium bromide	70
Sodium silicate	5
Magnesium sulphate	100
Sodium sulphate	25
Calcium phosphate	260
Calcium lactate	500
Bismuth salicylate	15
Albumin	25

Many German observers report that these patients do not tolerate codliver oil very well. With this fact in mind and thinking of the identical effect of ultraviolet rays and vitamine D in rickets we decided to use viosterol. Since the introduction of this diet at Muirdale the preparation, *Viosterol 100D*, has been given in doses of 3–7 drops, t.i.d.a.c. The following data are given by the Council on Pharmacy and Chemistry:

Viosterol 100 D is irradiated ergosterol in oil. Dissolved in a vegetable oil and standardized to contain 1333 rat units of vitamin D in each Gm., this strength being 100 times that of a potent cod liver oil used as standard. Viosterol is for use in the prophylaxis and treatment of rickets and, experimentally, in other conditions arising from faulty calcium and phosphorus assimilation. Viosterol does not contain vitamin A. Dosage: daily prophylactic dose for the average infant and child, 8–10 drops (0.1233 to 0.1666 cc.); for the premature and rapidly growing infant, 15 drops (0.25 to 0.333 cc.); in severe cases and for adults, doses in excess of 20 drops may be given.

The empirical use of codliver oil in tuberculosis and in the prevention of tuberculosis can be traced back for centuries. Its administration in 30–45-cc. daily doses to sanatorium patients was practised by many phthisiologists. The regular consumption of codliver oil by healthy adults during the winter months with the purpose of lessening susceptibility to colds has been advised recently. Since the publication of the work of Windaus and Hess (63) irradiated ergosterol is applied in the treatment of rickets, osteomalacia, tetany, and premature and fast-growing infants. In this connection the close relationship between vitamine D and the function of the parathyroid glands and the calcium level of the blood must be considered. It was demonstrated that codliver oil will increase the function of the parathyroid glands and by this means the calcium concentration of the blood. That such a favorable effect upon the calcium metabolism may be of great advantage in tuberculosis may be anticipated by the fact that the calcium requirement of a tuber-

culous organism is higher than that of the normal. Steenbock (64) states that excessive administration of vitamine D will increase the deposition of calcium and phosphorus in the various tissues of the body.

It is manifest from the above data that in the administration of the S. H. G. diet we are dealing with a complex problem. We tried to analyze its constituents separately to detect the influence of each; still it seems that further studies, clinical as well as experimental, are necessary to decide this question. It must not be forgotten that besides the diet and medication there are many other factors that may explain the reports of investigators which do not always substantiate the claims of the originators of this new method of treatment. The consideration of the type of cases, length of treatment, change in environment, overfeeding, more minute dietary provisions, proper symptomatic or special treatment, and, last but not least, the psychical effect should not be neglected in our evaluation.

More recent reports debate the acid-forming property of this diet, claiming that the basic values of the foods given are higher than the acid values. The first exponent of this opinion, Kroetz (65), was followed by others. Mecklenburg (66) found not only that the ash values of the given foods were alkaline but also that the alkali reserve of the blood was increased and the hydrogen-ion concentration of the urine decreased in patients on this diet. Whether, parallel to this increased alkalinity of blood and urine, similar or opposite changes occur in the body tissues should be the subject of further investigations.

We were deeply impressed by the therapeutic results in one of our patients who had been kept on a ketogenic diet over a period of seven months, the proportion of P:C:F being 1:1:5. This patient, a 34-year-old white female, was admitted to the Sanatorium with the diagnosis of genuine epilepsy and far-advanced pulmonary tuberculosis. The typical toxic symptoms were present for six months before admission. The entire left lung and the lower portion of the right lung were found to be involved by a granuloexudative process. Roentgenological and laboratory data corroborated the clinical diagnosis. Constitutional as well as local manifestations showed remarkable improvement at periodic examinations. She gained 13 kg. (29.2 lbs.), and her fever, rapid pulse and other toxic symptoms disappeared. Her pulmonary condition became apparently arrested. Since we did not exclude salt from the diet in this case, this patient has not been included in our analysis.

Out of 63 patients in whom special diet was attempted ten were not

analyzed because the diet was discontinued in less than a month. Four were discharged against medical advice in from one to three weeks from the inception of this diet; in six it had to be discontinued because of lack of appetite, nausea, recurring vomiting and weakness. It can be seen that in 10 per cent of those placed on this diet gastrointestinal disturbances and intolerable subjective symptoms rendered the continuation of this diet impossible. It is true that in two of these 6 patients there was evidence of intestinal tuberculosis. We found that patients with intestinal tuberculosis are able to adapt themselves to this diet with greater difficulty than patients with normal gastrointestinal function; and, if they are able to tolerate it, the chances for an improvement are less favorable than usually. Gerson states that this diet does not have an appreciable influence upon intestinal tuberculosis. Of 9 patients with pulmonary tuberculosis complicated by tuberculous enteritis two showed improvement and seven did not; and, of this seven, four died, one has progressive disease, and two remained stationary. Out of the 53 analyzed cases seven had gastrointestinal distress attributable to this diet. Vomiting, as a disagreeable sequence of this regimen, was noted by other observers. Loss of appetite following the institution of the diet was noticed in three patients, but we succeeded in overcoming this difficulty by the administration of dilute hydrochloric acid before meals. We think that this medicine could serve as a valuable adjunct in connection with this diet, and its use is warmly advocated on the basis of the clinical experience of Clairmont and ourselves, though Eimer (67) reports that the hydrochloric-acid secretion of the stomach does not suffer from the low salt content of the foods taken. On the contrary, he found that in the majority of cases there was a slight overproduction of hydrochloric acid. This result has been attributed to the raw constituents of the diet and an automatic decrease in the sodium-chloride excretion through the kidneys.

Out of 53 analyzed cases 50 had pulmonary tuberculosis, two renal tuberculosis, and one lupus vulgaris. The renal cases were kept on special diets for four and nine months respectively. Both of them had bilateral involvement. One of them died. The second renal case, a 31-year-old white male, has been under sanatorium care without improvement for one and a half years. The following methods of treatment were tried: Heliotherapy, tuberculin, sandalwood oil and caprokol, and bladder irrigations with 1 per cent methylene-blue solution. The patient developed a cold abscess in the right renal region in December,

1929, that was aspirated several times, the pus having been replaced by oxygen. This procedure proved to be inadequate, the abscess broke down, and a draining sinus remained. On special diet urinary symptoms improved, frequency and dysuria became less marked, and the renal sinus shows signs of healing with a gradually diminishing discharge. The patient's general condition also shows some improvement, though there is no increase in weight.

The following short abstracts of illustrative cases are given:

Case 8: White, male, 43 years, under sanatorium care with interruptions since 1917. *Diagnosis* on first admission: Advanced pulmonary tuberculosis involving the entire right lung, with cavitation. Had three-stage thoracoplasty in 1924, followed by considerable improvement. Readmitted to sanatorium after 3½-year absence. Complaints were moderate cough and expectoration, dyspnoea, chills, loss of strength and weight. The right side was found completely collapsed; numerous small moist râles were present in the left lower lobe; sputum positive. On salt-free diet for three months. General appearance improved, gained 2 kg. (4.5 lbs.) No râles detectable over the lungs. Special diet discontinued because patient complained of lack of appetite and abdominal pains. Gastrointestinal complaints persisted on regular diet, and roentgen study revealed adhesions at ileocaecal region.

Case 10: W. S., white, male, 22 years. *Diagnosis:* Advanced pulmonary tuberculosis involving entire right lung and left upper lobe. *Complaints:* Considerable cough and expectoration, haemoptysis, dyspnoea, malaise. Under sanatorium care without substantial improvement. On salt-free diet for three months. During this period gained 3 kg. (6.75 lbs.), and left lung showed less moisture than before. No change in cough, expectoration or constitutional symptoms. For this reason we were asked to discontinue the diet.

Case 11: J. G., white, male, 20 years. *Diagnosis:* Moderately advanced pulmonary tuberculosis involving both upper lobes. *Complaints:* Cough, slight expectoration, frequent haemoptysis, malaise. On salt-free diet for two months. The number of moist râles decreased in both lungs, and the roentgenograph showed considerable clearing in the right upper lobe. Weight, temperature, and pulse-rate remained stationary. Haemoptysis, that was quite frequent before, did not occur while on diet. Diet discontinued because of lack of coöperation.

Case 17: I. L., white, female, 34 years. *Diagnosis:* Moderately advanced pulmonary tuberculosis involving both upper lobes, with cavitation. *Complaints:* Moderate cough and expectoration, dyspnoea, thoracic pain, loss of

strength and weight. On special diet for seven weeks. Gained 2.5 kg. (5.6 lbs.). General appearance improved, and there was some clearing in the lungs.

Case 20: O. M., white, female. *Diagnosis* on third admission: Moderately advanced pulmonary tuberculosis involving both upper lobes. *Complaints:* Slight cough, expectoration, dyspnoea, fever, malaise, impaired digestion. During three-month period on special diet râles decreased on both sides, cough diminished, and temperature became lower; weight and pulse-rate remained stationary. Diet was discontinued because of a haemorrhage.

Case 22: L. K., white, female. *Diagnosis:* Advanced pulmonary tuberculosis involving entire left lung and right upper lobe, with cavitation. *Complaints:* Considerable cough and expectoration, thoracic pains, haemoptysis, chills, fever, night-sweats, loss of weight, and poor appetite. Given heliotherapy for three months with no improvement. On special diet during the last 11 months. During first half of this period the left lung was collapsed by artificial pneumothorax. This discontinued because of spontaneous pneumothorax and hydropneumothorax on same side. Showed remarkable improvement under dietetic regimen. Cough practically disappeared, there is no expectoration, toxic symptoms are absent, and appetite is good. No activity in either lung. Sputum became negative. Patient in excellent condition at present; found at last physical and roentgen examination that fluid in pleural cavity is also diminishing.

Case 23: A. S., white, female, 33 years. *Diagnosis:* Far-advanced pulmonary tuberculosis involving entire right lung and left upper lobe. *Complaints:* Considerable cough and expectoration, loss of weight, malaise, fever, lack of appetite, metrorrhagia. On special diet for 11 months. Gained 7 kg. (15.7 lbs.). Temperature and pulse are approaching normal, and digestive disturbances absent. Last examination showed quiescent lesion in less involved lung. At this stage a phrenic exairesis was performed on more diseased side.

Case 28: J. F., white, male. *Diagnosis:* Far-advanced pulmonary tuberculosis involving entire right lung and left upper lobe. *Complication:* Tuberculosis of right testicle. *Complaints:* Moderate cough and expectoration, thoracic pain, dyspnoea, loss of strength and weight. No change in pulmonary condition during first year of sanatorium stay. Developed cold abscess over sternum and in right testicle. Both abscesses broke down in spite of repeated aspirations, but the sinuses healed since patient was placed on special diet. General condition improved, and gained 1.5 kg. (3.3 lbs.). Roentgenograph of lungs shows some clearing.

Case 34: J. K., white, female. *Diagnosis:* Moderately advanced pulmonary tuberculosis involving entire left lung. *Complaints:* Cough and expectoration, malaise, abdominal pains. Under sanatorium care since June, 1928, with some improvement in general condition; still the extent and number of râles remained stationary. Stayed on special diet for five months. During this period general condition greatly improved, and cough and expectoration entirely cleared. Râles disappeared. Discharged apparently arrested.

Case 35: M. M., white, female. *Diagnosis:* Far-advanced pulmonary tuberculosis involving entire right lung and left upper lobe. *Complaints:* Moderate cough and expectoration, fever, loss of weight, dyspnoea, malaise. Under sanatorium care since 1927. Shortly after admission had phrenic-nerve block. When this procedure did not result in satisfactory improvement, artificial pneumothorax was instituted and continued for one year, having been discontinued because of pleural effusion. Following this given graded heliotherapy without good results. Due to toxic symptoms transferred to infirmary and placed on special diet. During first month on this diet she lost 2 kg. (4.5 lbs.). Later on regained weight that has remained stationary since. According to recent examination the toxic symptoms have abated, temperature is practically normal, and appetite very good. Process in left lung became quiescent, and right side shows marked signs of fibrosis with only slight activity. On special diet for 8 months.

Case 38: F. M., white, male. *Diagnosis:* Far-advanced pulmonary tuberculosis involving entire right side with cavitation. *Complaints:* Moderate cough and expectoration, malaise. Under sanatorium care for 1½ years before special diet was instituted. Artificial-pneumothorax treatment for one year; discontinued because of pleural effusion. Due to patient's stationary condition, placed on salt-free diet for three months. During this period gained 1.5 kg. (3.3 lbs.), pulmonary activity decreased, cough and expectoration became less, and general condition appeared very satisfactory. Sputum became negative. Left institution against medical advice.

Case 39: S. J., colored, male. *Diagnosis:* Far-advanced pulmonary tuberculosis involving entire right lung and left lower lobe. *Complaints:* Moderate cough and expectoration, malaise. Artificial pneumothorax on right side for 1½ years; discontinued because of pleural effusion. Pulmonary condition remained practically unchanged. At the time when placed on special diet, numerous moist râles throughout right lung and left lower lobe. After eight months on this diet physical examination showed no activity on left side and diminution in number and size of râles on right side. Temperature, cough and expectoration remained same. Weight stationary. Patient's general condi-

tion very good. Due to the clearing of better side, decided to perform phrenic-nerve block on more involved side.

Case 44: F. L., white, male. *Diagnosis:* Moderately advanced pulmonary tuberculosis involving both upper lobes. Under sanatorium care since 1924. Both lungs showed some clearing during first two years. Condition stationary since. On special diet since January, 1930. Last physical examination revealed signs of clearing in both lungs, particularly right side. Pulmonary process gives impression of arrested fibrotic lesion with secondary bronchiectasis. Cough diminished, while weight same as before.

Case 45: J. D., white, male. *Diagnosis:* Far-advanced pulmonary tuberculosis involving both uppers, right middle and left lower lobe. Under sanatorium care with short interruptions since 1918. In 1929 activity on left side abated, and phrenic-nerve block performed on right side. No improvement following operation. On the contrary, five months later again developed activity on better side. Complaints at that time were considerable cough and expectoration, malaise, and marked dyspnoea. Since placed on special diet in January, 1930, cough and expectoration markedly decreased, and extent and number of râles found diminished on last examination.

Case 47: G. B., white, male. Under sanatorium care from December, 1923, to August, 1928, and from December, 1928, to present. Had phrenic exairesis and three-stage thoracoplasty on right side, and discharged as apparently arrested in 1928. Had flare-up following influenza, and under routine care after readmission. At that time had slight cough, moderate expectoration, dyspnoea, thoracic pains, and night-sweats. Pulmonary findings showed medium-sized moist râles in right upper lobe. On special diet for 8 months. Gained 2 kg. (4.5 lbs.). General appearance greatly improved. Has no constitutional or local symptoms. Pulmonary condition is considered at least quiescent.

Case 49: M. K., white, female, 24 years. *Diagnosis:* Far-advanced pulmonary tuberculosis involving entire right lung and left upper lobe. *Complaints:* Moderate cough and expectoration, malaise. Under routine care for 9 months; no improvement during that period. Bilateral artificial pneumothorax in April, 1930. At same time salt-free diet was started. General and pulmonary condition rapidly improved since. Gained 12 kg. (27 lbs.). Number of râles markedly diminished in both lungs. Sputum became negative. Has very slight cough and expectoration. Constitutional symptoms absent.

Case 50: N. O., white, female, 62 years. *Diagnosis:* Far-advanced pulmonary tuberculosis involving entire left lung and right upper lobe, with cavitation.

Complaints: Moderate cough and expectoration, fever, malaise, loss of weight. Placed on special diet after three-month stay at sanatorium because of lack of improvement under routine care. During last five months general condition slowly improved, cough and expectoration diminished. Sputum became negative. No change in physical findings.

Case 55: J. L., white, male, 30 years. Under sanatorium care with exudative pulmonary tuberculosis involving both upper lobes from 1919 to 1924, when discharged as apparently arrested. Readmitted in June, 1929, with reactivation in both upper lobes and with large cavity in left upper lobe. *Complaints:* Cough, expectoration, chills, fever, night-sweats, loss of weight, malaise, digestive disturbances. After short period of improvement a rapid spread of process set in. Entire both lungs showed moist râles, and impairment was

TABLE 1

	CASES
All lobes	13
Entire right lung, left upper lobe	10
Both upper, right middle, left lower lobe	6
Both upper, right middle lobe	2
Both upper, left lower lobe	5
Both upper lobes	6
Entire right lung	2
Right upper and middle lobes	1
Right upper lobe	2
Entire left lung	2
Left upper lobe	1

present over both upper lobes. Cough and expectoration greatly increased, blood-streaks were visible in the sputum continuously, and patient complained of thoracic pains and dyspnoea. Artificial pneumothorax instituted in November, 1929, and continued till June, 1930, without any beneficial effect. Discontinued because of pleural effusion. Remained febrile and presented all symptoms of marked toxicity. Started on salt-free diet on June 7, 1930. Temperature gradually decreased, till normal in three weeks. Other symptoms of toxicity abated. Started to gain in weight during third month on diet. Sputum became negative.

Out of the 50 pulmonary cases 41, or 82 per cent, had far-advanced, and 9, or 18 per cent, moderately advanced tuberculosis. The distribution of the pulmonary involvement is given in table 1.

The following complications were noted: Tuberculous enteritis, 9; tuberculous laryngitis, 4; bone and joint tuberculosis, 3; spontaneous

pneumothorax, 1; hydropneumothorax, 3; tuberculous pyopneumothorax, 1; pleurisy, 1; tuberculous peritonitis, 1; psoas abscess, 1; genitourinary tuberculosis, 3; perinephritic abscess, 1; allergic asthma, 1; metrorrhagia, 1; epilepsy, 1.

It may be thought that such types of patients might have represented, *a priori*, a poor prognosis and very little if any chance for therapeutic results. Still the selection of cases was done purposely, with the idea in mind to study the effect of this diet upon the symptoms and course of the disease rather than to try to accomplish a cure of the tuberculosis.

The course of the disease, its relation to the length and type of treatment, and the end-results are presented in table 2.

It can be seen from table 2 that of the 50 pulmonary cases 15, or 30 per cent, died, the condition became worse in 6, or 12 per cent, 11, or 22 per cent, remained stationary, 15, or 30 per cent, improved, 2, or 4 per cent, became quiescent, and 1, or 2 per cent, apparently arrested. Altogether 18, or 36 per cent, of the pulmonary cases were benefited.

Favorable changes in symptoms and signs occurred as follows:

	per cent
Decrease in cough in 10	20
Decrease in expectoration in 9	18
Sputum became negative in 5	10
Decrease in number of râles in 14	28
Roentgenographic clearing in 8	16
Decrease in temperature in 6	12
Increased appetite in 7	14
Increased weight in 9	18

It is worth while to mention that in some of our patients some of these changes appeared in a few weeks following the institution of this diet. Anyone who is familiar with the particular mental attitude of our patients will realize that these results cannot be due to suggestion. We experienced a great deal of scepticism, lack of confidence and interest, and resistance against this new method of treatment.

It usually takes from two to three weeks for the average patient to accustom himself to the salt-free diet. We think that the generous use of spices, within compatibility with the patient's condition, will help us to overcome the difficulties of the first few weeks. The tolerance of patients to salt-free meals is very variable. Some of them are conscious of the salt deficiency throughout the treatment, but the majority will take it just as easily as the regular diet. In one of our cases, when the diet was discontinued after three months, the patient stated that he

TABLE 2

NUMBER	NAME	CLASSIFICATION	COMPLICATIONS	PREVIOUS TREATMENT	SIMULTANEOUS TREATMENT	ON DIET		RESULT
						From	To	
1	A. U.	Adv.	Pott's disease, psoas abscess	Bradford frame	Bradford frame	9/ 5/29	11/ 5/29	Died
2	C. E.	Adv.	Pyopneumothorax		Rib resection	9/ 5/29	3/23/30	Died
3	P. N.	Moderat. adv.	Multiple bone tuberculosis	Quartz lamp	Quartz lamp; roentgen ray	9/ 5/29	11/ 8/29	Died
4	J. D.	Moderat. adv.				9/ 5/29	12/ 7/29	Worse
5	J. L.	Adv.				9/ 5/29	12/ 5/29	Worse
6	C. Q.	Adv.				9/ 5/29	12/ 5/29	Died
7	A. B.	Adv.	Tuberculous enteritis		Phrenic block; pneumoperitoneum	9/ 5/ 29	12/15/29	Stationary
8	A. R.	Adv.	Tuberculous peritonitis	Three-stage thoracoplasty		9/ 7/29	12/17/29	Improved
9	P. K.	Adv.	Renal, intestinal, pleural tuberculosis	Pneumothorax; nerve block		9/ 7/29	11/ 6/29	Died
10	W. S.	Adv.				9/ 7/29	12/17/29	Improved
11	J. G.	Moderat. adv.	Tuberculous enteritis			9/ 7/29	11/ 8/29	Improved
12	A. B.	Adv.	Renal tuberculosis	Pneumothorax		10/19/29	11/16/29	Died
13	E. M.	Adv.				10/19/29	1/ 1/30	Worse
14	M. M.	Adv.		Thoracoplasty		10/19/29	3/22/30	Worse
15	A. L.	Adv.	Tuberculous laryngitis			10/19/29	12/17/29	Died
16	S. G.	Adv.		Phrenic n. block		10/19/29	12/ 6/29	Died
17	I. L.	Moderat. adv.				10/19/29	12/ 8/29	Improved
18	M. S.	Adv.	Tuberculous laryngitis			10/19/29	3/20/30	Died

19	A. W.	Adv.	Tuberculous enteritis	Pneumothorax		10/19/29	12/ 5/29	Died
20	O. M.	Moderat. adv.				10/19/29	1/29/30	Improved
21	E. K.	Adv.	Intestinal tuberculosis, hydropneumothorax			10/19/29	12/ 5/29	Died
22	L. K.	Adv.	Hydropneumothorax	Heliotherapy	Pneumothorax	10/19/29	to date	Improved
23	A. S.	Adv.	Metrorrhagia			10/19/29	to date	Improved
24	R. B.	Adv.				10/22/29	8/ 4/30	Died
25	F. P.	Adv.	Hydropneumothorax			11/ 5/29	12/ 7/29	Died
26	A. L.	Adv.	Tuberculous laryngitis and enteritis		Pneumoperitoneum	11/ 5/29	12/ 7/29	Died
27	P. S.	Renal	Perinephritic abscess, cystitis	Tuberculin, heliotherapy, local treatment	Heliotherapy	12/ 5/29	to date	Stationary
28	J. F.	Adv.	Bone tuberculosis, tuberculous testicle	Heliotherapy		12/ 5/29	to date	Improved
29	Less than a month on special diet							
30	R. B.	Adv.				12/ 5/29	1/10/30	Died
31	Less than a month on special diet							
32	R. M.	Adv.	Tuberculous laryngitis	Pneumothorax		12/14/29	to date	Stationary
33	O. Z.	Renal	Tuberculous cystitis	Heliotherapy		12/17/29	4/14/30	Died
34	J. K.	Moderat. adv.				12/22/29	5/29/30	Apparently arrested
35	M. M.	Adv.				1/18/30	to date	Improved
36	Less than a month on special diet							
37	F. H.	Adv.	Intestinal tuberculosis	Pneumoperitoneum		1/18/30	5/18/30	Stationary
38	F. M.	Adv.		Pneumothorax		1/18/30	4/27/30	Improved
39	S. J.	Adv.		Pneumothorax		1/18/30	to date	Improved
40	J. S.	Adv.				1/18/30	to date	Stationary
41	Less than a month on special diet							
42	F. M.	Adv.	Allergic asthma			1/18/30	to date	Stationary
43	Less than a month on special diet							

TABLE 2—*Concluded*

NUMBER	NAME	CLASSIFICATION	COMPLICATIONS	PREVIOUS TREATMENT	SIMULTANEOUS TREATMENT	ON DIET		RESULT
						From	To	
44	F. L.	Moderat. adv.				1/18/30	to date	Quiescent
45	J. D.	Adv.		Phrenic-nerve block		1/18/30	to date	Improved
46	S. N.	Adv.		Phrenic-nerve block; heliotherapy		1/18/30	4/10/30	Stationary
47	G. B.	Moderat. adv.		Thoracoplasty		1/18/30	to date	Quiescent
48	J. K.	Adv.	Epilepsy, intestinal tuberculosis	Pneumothorax; phrenic-nerve block		2/ 8/30	6/26/30	Worse
						2/ 8/30	6/26/30	Worse
49	M. K.	Adv.			Bilateral pneumothorax	4/15/30	to date	Improved
50	N. O.	Adv.				4/15/30	to date	Improved
51	Less than a month on special diet							
52	Y. W.	Adv.	Tuberculous testicle			6/ 5/30	to date	Worse
53	Less than a month on special diet							
54	E. W.	Adv.				6/ 5/30	to date	Stationary
55	J. L.	Adv.	Intestinal tuberculosis	Pneumothorax		6/ 5/30	to date	Improved
56	J. W.	Moderat. adv.		Heliotherapy		6/ 5/30	to date	Stationary
57	Less than a month on special diet							
58	M. G.	Adv.				6/16/30	to date	Stationary
59	Less than a month on special diet							
60	Less than a month on special diet							
61	E. P.	Adv.				6/16/30	to date	Stationary
62	F. K.	Adv.		Pneumothorax		7/ 5/30	to date	Stationary
63	J. M.	Lupus		Heliotherapy; gold; roentgen ray		7/ 5/30	to date	Improved

was unable to take regular diet because of its allegedly disagreeable salty taste, and requested to be placed again on salt-free diet.

SUMMARY

1. The Sauerbruch, Hermannsdorfer, Gerson diet is a complex and technically difficult, still an applicable, therapeutic measure.

2. Its use should be restricted to institutions with well-trained personnel, well-organized service, and adequate technical facilities, to avoid its abuse and unethical commercialization.

3. Its clinical value being under investigation, the deductions presented from different sources must be analyzed with due regard to the type of cases, length of treatment, additional medical or surgical measures, and eventual variations in the diet itself.

4. Changes in the reaction of blood and tissue juices under the effect of this diet are so irrelevant that it seems improbable that they could exert any profound influence upon the vital functions of the organism. Assuming that sodium and chlorine weaken certain chemical and biological functions of the cells, the absence of salt from the diet may create a favorable condition for effective resistance, defense and repair. We consider also the high vitamine-D and calcium intake as essential features of this regimen.

5. Individual consideration of each case must not be lost sight of.

6. Great variations as to tolerance of the diet and medication were met with.

7. The administration of dilute hydrochloric acid before meals may improve the gastrointestinal function of the patient.

8. This diet should not be considered as specific or curative for tuberculosis. It is only ameliorative in the sense that it stimulates the tissue cells to more intensive vitality and more efficient immunological response. It cannot substitute but only supplement our standard measures.

9. Favorable results were seen in 36 per cent of our pulmonary cases. Gain in weight, decrease in cough, expectoration, temperature and pulse-rate, improved appetite, and complete or partial abatement of subjective and objective symptoms were recorded.

10. Considering the fact that 82 per cent of our pulmonary cases had far-advanced tuberculosis, with serious complications in many instances, we feel that the beneficial results found justify the further application of the Sauerbruch, Hermannsdorfer, Gerson diet in the treatment of tuberculosis.

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VITAMINE THERAPY IN PULMONARY TUBERCULOSIS[1]

I. THE EFFECT OF ACTIVATED ERGOSTEROL ON THE CALCIUM AND INORGANIC PHOSPHORUS IN THE BLOOD-SERUM

PAUL D. CRIMM

The study of the effect of activated ergosterol as a therapeutic agent in pulmonary tuberculosis resolves itself into the correlation of three avenues of investigation. The clinical picture, analyses of the blood, and the pathological changes revealed by the stereoscopic roentgenogram are the methods limited by using the human body as a test-tube.

Pulmonic tissue is the medium which is being utilized by the tubercle bacilli. Their growth on this medium produces certain chemical and immunological reactions which are interpreted grossly by the objective and subjective symptoms of the host. In the light of scientific research we are not prone to interpret the merits and demerits of any therapeutic product on clinical interpretations *per se*, since the combinations of many intricate chemical complexes are available, although all are not determinable, to substantiate our clinical interpretation. In addition to the clinical response and the X-ray, we have only employed to date the serum-calcium and serum-phosphorus as an index for corroborative information.

THE PROBLEM OF CALCIFICATION

The calcification of the tubercle has long been considered one of the end-results of the constructive forces in the healing of tuberculous infection in tissue. The question arises as to whether the calcified tubercle is the resultant of a proper chemical reaction which the constituents of the blood supply, or whether it becomes calcified as a final process often exhibited by necrotic tissue. Wells (1) says that calcium salts are only deposited in necrotic tissue. It is common knowledge that certain pulmonary tubercles calcify spontaneously while others excavate their contents. The work of Smith (2), and Levaditi and Li Yuan Po (3), would tend to disprove the necrotic-tissue theory in part, since these investigators showed in animals that calcium deposits are found in certain viable

[1] From the Boehne Tuberculosis Hospital, Evansville, Indiana.

tissues. Spies (4) found that animals showed calcium deposits in arterial walls, lungs, kidneys, stomach wall, heart muscle, bronchial cartilage, spleen, ovary and adrenal tissue, but he did not find any in the liver or striated muscle. This heterotopic calcification was brought about with massive doses of viosterol.

A further significant fact brought out by the work of Spies (4) was that some tubercles did not calcify although they were of the same age as those that did calcify. Clinicians have long observed this fact in the healing of pulmonary tuberculosis, not so much as to the age of the lesions as to the character of repair. Certainly, if every tubercle could utilize calcium in its process of repair, before it passed into a stage of extensive destruction, in the form of cavitation, the problem of healing would be simplified.

In children calcification is rarely seen under the age of two years. But, at the same time, regardless of the length of time it requires for such a chemical deposition, the tubercles in the pulmonary tissue of the child, as a rule, show calcification as one of the prominent end-results. Even apical lesions in children demonstrate calcium deposits not infrequently. It could be only vaguely assumed, since children are more subject to disorders of calcification than adults, that this unbalanced or a more responsive tendency to such a repair would be the cause of calcification. The physiological process of haemostasis (5) is the fundamental metabolic exchange to keep in mind when solving any problem like the mechanics of calcification. It must be considered in the therapeutic application of any agent which might promote more rapid healing of pulmonary tuberculosis.

CALCIUM TIMES PHOSPHORUS PRODUCT

Peters and Eiserson (6) report that the concentration of calcium varies directly with the concentration of protein and inversely with the concentration of inorganic phosphorus. They also say that it is impossible to interpret serum-calcium variations accurately unless protein or inorganic phosphorus are simultaneously determined. On the other hand, they state that calcium should not be directly related to phosphorus at all but to some complex function of phosphorus which would be affected by the pH. Their sera were obtained from nephritic patients in whom they did not suspect any defective calcium metabolism. Whether these observations would hold true in cases in which calcium metabolism was abnormal has not been determined.

It is evident that, even without the consideration of the influence of the protein molecule, the relation of calcium and phosphorus in the blood is more significant than the consideration of calcium alone. Warkamy and Wasitzky (7) in rabbits found that the phosphataemic curve increased in from 24 to 48 hours after the use of irradiated ergosterol (50 mgm.), but an increase in the fasting values for calcium within the same time could not be established with certainty. To study the two as individual units does not give us a fair indication of the given therapeutic effect. Neither does a single determination in a twenty-four-hour period give us an exact interpretation of the dilute solution's value for that entire period, much less for a subsequent period of time. Multiplication of the calcium and phosphorus determinations gives us a product of their relations. The product, Ca × P, presents us with a more accurate picture of the calcium-phosphorus metabolism. This is illustrated in table 1, chart 5D and chart 4E. Howland and Kramer (8) used the product of Ca × P in rickets. They stated that, if the product was below thirty, rickets occurred; between thirty and forty it was probable; above forty healing is taking place, or rickets is absent. Even though this work is in dispute, we would probably not be able to use such a scale in pulmonary tuberculosis, but so far it can be used as the best indicator in comparing any elevation of the concentrates with those normal.

NORMAL CONCENTRATIONS OF CA AND P IN THE BLOOD-SERUM

Sweany, Weathers and McCluskey (9) found that calcium was about normal in all stages of tuberculosis: that is, 9 to 11 mgm. calcium per 100 cc. They found lecithin phosphorus was decreased and acid-soluble phosphorus increased in severe cases. Lecithin phosphorus was increased in improved cases. Matz (10) discovered a little variation in the blood-calcium content in different stages of the disease. Looft (11) found a slight increase in beginning and moderately advanced cases. Brockbank (12) noted that neither age nor sex influenced serum calcium. His arrested cases showed a high calcium and acute cases a low calcium. Halverson, Mohler and Bergheim (13) reported that calcium values did not increase over normal figures with a high calcium diet. No marked deviations were observed in the calcium content of the serum from patients in the various stages of pulmonary tuberculosis. Improving patients showed slightly higher averages than the unimproved. In the advanced cases they observed the greatest variations, some having high values, while others had low values.

We have found the normal range of calcium in pulmonary tuberculosis to be as a rule from 8.5 to 11.5 mgm. per 100 cc. of blood-serum, with the majority bordering on the upper limit. Other metabolic processes being equal, any patient who is able to take care of a normal dietary intake will in a twenty-four-hour average have a normal calcium and phosphorus range. Seventy-five normal calcium determinations of 30 patients in various stages of tuberculosis, the majority being in stage two or three, had an average calcium concentration of 10.24 mgm. and a phosphorus concentration of 3.6 mgm. Fifteen of thirty had three normal determinations and the other half had two normal determinations at periodic intervals. We do not agree with Dolgopol (14) that the serum calcium below 9.2 mgm. per 100 cc. is a sign of imminent death. We found the calcium concentration of 6 healthy men, the blood sample being taken after breakfast, to have an average of 8.4 mgm. of calcium and a phosphorus content of 3.4 mgm. per 100 cc. Three months later the same 6 men had an average calcium value of 10.8 mgm. and an average phosphorus value of 3.7 mgm. This goes to show that the Ca:P ratio constantly varies within normal limits, and that several normal determinations must be performed before considering any effect for a specific agent. In a series of cases presented in table 1, serum calcium-phosphorus normals were obtained in the beginning, then at sixty days, and then at the end of one hundred and twenty days, and the average of three concentrates was considered to be more characteristic for that particular individual, even more so than two normal determinations three or four days apart. In addition to the establishment of normals for each individual case, since this is essentially prerequisite, other controls who received no accessory vitamine, other than that in the regular hospital diet, were maintained.

CALCIUM AND PARATHORMONE THERAPY

The study of the different calcium levels of the blood in various types of tuberculous patients gave impetus to the use of calcium salts as a therapeutic agent designed to influence calcium metabolism. Maver and Wells (15) found that the oral administration of calcium salts did not increase the quantity of calcium in the blood and tissues in experimental tuberculosis, while Matz (10) obtained a rise of serum calcium after oral administration.

Teplitz (16) found no increase in serum calcium in tuberculous patients after an administration of calcium lactate combined with thyroid extract.

TABLE 1

Showing the serum-calcium and serum-phosphorus concentration before and after treatment with Viosterol 250-D: mgm. of calcium and phosphorus per 100 cc. of blood-serum

CASE NUMBER	AGE	STAGE	PRELIMINARY NORMALS		30 DAYS LATER; AFTER FEEDING VIOSTEROL 250-D; DOSAGE 15 DROPS, B.I.D.		60 DAYS LATER; 30 DAYS WITHOUT VIOSTEROL 250-D		90 DAYS LATER; 30 DAYS WITH VIOSTEROL 250-D; DOSAGE 15 DROPS B.I.D.		120 DAYS LATER; 30 DAYS WITHOUT VIOSTEROL 250-D		AVERAGE OF NORMALS, PROVIDING NO ACCUMULATIVE EFFECT IS PRESENT 30 DAYS AFTER A 30-DAY FEEDING		NORMAL Ca × P PRODUCT	AVERAGE AFTER TWO 30-DAY PERIODS OF VIOSTEROL 250-D; DOSAGE 15 DROPS B.I.D.		AFTER VIOSTEROL Ca × P PRODUCT
			Serum Ca	Serum P	Serum Ca	Serum P	Serum Ca	Serum P	Serum Ca	Serum P	Serum Ca	Serum P	Serum Ca	Serum P		Serum Ca	Serum P	
744	17	I	11.9	5.0	12.9	5.5	11.2	4.0	12.4	5.3	11.6	3.5	11.56	4.16	48.09	12.65	5.40	68.31
746	20	II	11.8	5.0	12.9	5.0	12.4	4.5	12.6	5.4	11.0	4.0	11.76	4.46	52.45	12.75	5.20	66.30
659	54	II	10.9	3.5	11.7	4.5	10.2	3.0	11.1	3.3	10.7	3.0	10.60	3.16	33.49	11.40	3.60	41.04
705	18	III	9.3	3.0	11.0	5.0	10.4	4.0	12.4	4.5	11.1	4.0	10.26	3.60	36.93	11.70	4.75	55.57
446	35	III	10.6	3.2	11.0	4.5	10.4	3.3	10.9	4.0	10.3	3.3	10.36	3.26	33.77	10.95	4.25	46.53
536	45	II	11.1	4.0	11.9	4.5	10.3	4.0	10.0	3.5	9.0	3.5	10.13	4.16	42.14	10.95	4.00	43.80
556	43	III	11.3	3.5	12.1	5.5	11.8	3.0	11.4	4.0	10.5	3.5	11.30	3.33	37.62	11.75	4.75	45.81
658	24	III	11.3	3.5	12.9	5.0	12.6	4.0	12.4	5.5	10.9	3.0	11.60	3.50	40.60	12.65	5.25	66.41
749	18	II	10.6	4.5	11.1	5.0	11.3	4.5	11.4	4.7	10.7	4.0	10.86	4.33	46.02	11.25	4.85	54.56
698	50	III	10.8	4.0	11.4	4.5	11.3	4.0	11.4	3.5	11.2	3.5	11.10	3.86	42.84	11.40	4.00	45.60

Numerous investigators also attempted to promote calcification by the use of calcium salts, but the consensus of opinion concluded that such was a doubtful therapy. Burgess and Cantarow (17) administered parathyroid extract and calcium lactate and also parathyroid alone, but their results showed no change in the calcium and in the lung fields. They obtained a hypercalcaemia of 1 to 3 mgm. per 100 cc. of the blood. Learner (18) obtained the best results with parathormone injections on dogs. Dependent upon the doses of the subcutaneous and intramuscular injections, the blood-serum calcium was raised over 100 per cent.

Stewart and Percival (19) showed that parathormone raised the calcium in the blood-serum, even when the factor of any influence of absorption or excretion was eliminated by evisceration. They agreed with Greenwald and Gross (20) that calcium came from the soft tissues or bone or both. Gross and Greenwald (20) came to the conclusion that the administration of parathyroid extract led to increased excretion in the urine and faeces of phosphorus and calcium and that the increased excretion is able to continue for a long time. They found that cats, rabbits and rats were more resistant to huge doses than dogs.

Although calcium therapy failed to produce any results or the use of parathyroid extract failed to reveal the mechanism of calcium metabolism, it has at least given us the information that it is a very complicated problem with many intangible chemical relationships. Ultimately, we may have to put the mechanism of hypercalcaemia brought about by an oral administration of activated ergosterol in the same category. Nevertheless, it is being used extensively as a therapeutic adjunct in tuberculosis. For this reason we have a great many clinical reports seemingly satisfactory, although many have not been verified by laboratory or experimental study. Until a better understanding of calcium-phosphorus metabolism reveals itself, undoubtedly we can establish a higher but safe dosage control just below the border line of hypercalcaemia.

THE THERAPEUTIC AIM OF ACTIVATED ERGOSTEROL

As Hess, *et al.* (21), have pointed out, activated ergosterol, in causing an excess of calcium, is simply a sign of an overdose of an antirachitic agent, which also may result from large doses of codliver oil. Kramer, *et al.* (22), after the administration of ergosterol for twelve months, found no increase in either serum or phosphorus. Here again the Ca × P product was not used to substantiate their results. Grant, *et al.* (23), concluded from experiments that white rats were made susceptible to

tuberculosis by decrease of calcium and vitamine D in the diet. So, in pulmonary tuberculosis it is the aim to produce with activated ergosterol an excess of calcium-phosphorus above normal, so as to maintain sufficient storage of these elements, or to avoid normal fluctuations of the concentrations to the lower serum levels. At the same time, we do not desire to cause the toxic symptoms of either a hypercalcaemia or a hyperphosphataemia. By studying the effects in building up an increased quantity of calcium and phosphorus without disturbing the regulatory mechanism, as in the parathormone experimentation or in overdosage of viosterol, concurrent evidence may add information to the subject.

Simonent and Tauret (24) found that viosterol caused a rapid increase in the percentage of calcareous salts in lung tissue. The increase was 1:20 in healthy and 1:80 in tuberculous rabbits. The percentages of calcareous salts in the lungs of tuberculous rabbits not given viosterol was not stated. Hess and Lewis (25) in infants and animals, Pfansthiel (26), Krütmer and Moll (27), Harris and Moore (28), and Klein (29) in animals, reported that massive doses of irradiated ergosterol resulted in manifestations of toxic reactions. On the whole, the earliest symptoms were loss of appetite, and later impaired nutrition, loss of weight, hypercalcaemia and abnormal calcium deposits. Dixon and Hoyle (30) did not, however, observe any pathological effects.

In judging reports one must keep in mind the variation in strength of different activated ergosterol preparations. Therapeutic doses in cases of pulmonary tuberculosis have so far enjoyed a good margin of safety. The serum calcium-phosphorus determinations, together with the Ca × P product, are certainly a check on the dosage indicated or contraindicated, and, in the meantime, should be the chief guide in the evaluation of either symptoms or results. Our work tends to prove that many of the early symptoms, occurring in the administration pro or con, are unwarranted, since no radical change occurred in the serum-calcium and serum-phosphorus concentrations.

In the early administration of viosterol[2] to tuberculous patients, the psychological effect should rightly be ignored. One can obtain a symptomatic report which fairly balances between increased or decreased appetite, nausea, cough, ease of expectoration, production of sputum, and weight. One patient noticed more frequent bowel movements which

[2] Viosterol is the nonofficial designation given to irradiated ergosterol in new and nonofficial remedies. The preparation used here was viosterol 250 D, N. N. R., Mead Johnson and Company.

was probably not correct. We did notice, however, that, if sunshine therapy and viosterol were given simultaneously, there occurred increased cough and expectoration. For some reason or other, the patient does raise sputum seemingly more easily provided the quantity is considerable, or if the quantity is small they complain of its being more tenacious. Case 748, chart 1, was of a patient who had one hour of sunshine daily for thirty days prior to the feeding of viosterol. The sunshine was continued and 10 drops of viosterol, b.i.d., were given for thirty days. The patient complained of increased cough and expectoration. A lower calcium determination was recorded, and after thirty days of rest from both the drug and sun this calcium resumed a higher elevation. The thirty-day treatment with viosterol was again instituted, but without sun, and another drop in calcium occurred. During this period the patient did not have any increase in cough or expectoration. The concentration was undoubtedly within normal range, and it is doubtful if any significance can be attached to such a curve except to demand repetition of the experiment.

In table 1, in our group of 10 cases which were given 15 drops, b.i.d., of viosterol 250 D, for thirty continuous days, omitted for a rest period of thirty days, and then repeated thirty days followed by a subsequent rest period, totalling a period of one hundred and twenty days of direct observation with sixty days of therapy intermittent with thirty days' rest period, no adverse results were obtained. Two patients had haemorrhages during the administration of viosterol, but, since they had had them previously, viosterol was continued with no increase in the number or quantity of haemorrhages. A few patients thought they had improved more rapidly during the thirty-day period of rest for having had the thirty-day feeding period. Whether the subjective symptoms in the beginning were due to the patient's Ca:P mechanism becoming regulated to activated ergosterol can only be interpreted by the fact that no subjective symptoms occurred that could not be attributed to anything but the vicissitudes of pulmonary tuberculosis.

Objectively all 10 patients in table 1 had, at the end of one hundred and twenty days, a lower average of temperature and pulse. Physical and X-ray findings remained unchanged or improved. All patients had an increase in their calcium and phosphorus, although cases 698 and 536 received little response as proved by the product Ca $\times$ P. The average normal Ca $\times$ P product of the 10 cases was 40.90, while the average Ca $\times$ P product after viosterol was 53.39. To say whether a slight excess of calcium or phosphorus materially hastened the improvement, or pre-

vented retrogression, would not be conservative in view of the number of patients thus far studied. We know contraindications of its determinations were consistently absent and the potency of such a dose of codliver oil, as far as vitamine D is concerned, makes it an admirable therapy since many tuberculosis patients are exceedingly intimate with gastric disturbances.

Kaminsky and Davidson (31) used 20 drops of viosterol 100 D, every day for 7–10–12 days on ten patients with pulmonary tuberculosis, and the serum concentrations increased on a range from 1.08 to 6.4 mgm. per 100 cc. of blood-serum. Chart 5B and chart 4C demonstrate that the lower border of high calcium can be obtained with milk alone. In comparing the Ca × P products in charts 5D and 4E one can readily see that the products of one calcium and phosphorus determination could reveal a range of calcium above another similar determination, but if the average products of several comparative determinations are considered our results are definitely checked. The Ca × P product of normals before and after feeding must necessarily be known to prove that the individual concentrations actually show such an elevation. Thus, our experimentation does not show such an increase in so short a period of time. The difference, of course, may be due to the milk intake and diet. It cannot be due to the drug, since our viosterol had a greater potency. Our patients average from 4 to 8 glasses (250 cc. per glass) of pasteurized milk a day. So far, on our regular hospital diet, we believe that the substantial rise of calcium, and possibly phosphorus, calls for at least a twenty-day feeding of 15 drops, b.i.d., as far as viosterol 250 D is concerned.

In fact we believe that, on our diet and with this potency and dosage, high calcium values are produced only at the expiration of thirty days. Chart 3, for example, did not show over 12.7 mgm. of serum calcium until between the sixtieth- and ninetieth-day period of continuous feeding, when the calcium concentration reached 14.5 mgm. The patient was then put on a rest period, even though he had no symptomatology. We might state, however, that, in a series not reported herein, we have found slight nausea and anorexia to occur when the calcium concentration reached 16 mgm. This may not hold true for every case. Chart 2 shows two normal readings two days apart, a lowering of the calcium after five days and a further decrease to 9 mgm. on the twentieth day. Between the twenty-seventh and forty-fifth day it reached 13.4 mgm. without symptomatology.

Case 771, chart 3, was on a regimen of absolute bed-rest for seven

months prior to taking viosterol and did not gain weight. During the first thirty-day period of feeding he gained 12 lbs., and in the remaining sixty-one days he gained 12 lbs. The addition of vitamine D may have acted as a catalyzer in accounting for the addition of weight. Other patients did not gain, but otherwise improved or remained stationary on viosterol; so there is evidently a lack either of the proper combination or utilization of such elements required for gaining weight. Case 800, chart 2, gained 4 lbs. in weight during the first twenty-seven days of viosterol feeding, although this gain might have been due to constant bed-rest. From the twenty-seventh to the forty-fifth day the patient lost the 4 lbs. gained, which he attributed to one dose of Epsom salts. Viosterol is being continued on this patient.

MODE OF ACTION OF ACTIVATED ERGOSTEROL

There has been considerable discussion as to whether activated ergosterol elevates the calcium by obtaining it from bone and tissue, or whether in the main it is derived from the gastrointestinal tract. Experiments illustrated in charts 4 and 5 are certainly not foolproof, but they give us the impression that the elevation of calcium and phosphorus in the blood, following the feeding of viosterol, is due to an increase in the absorption and assimilation from the gastrointestinal tract. Bauer and Marble (32) suggest that irradiated ergosterol increased the amount of calcium absorbed from the gastrointestinal tract. Likewise, Kaminsky and Davidson (31) interpret the effect of the ingestion of irradiated ergosterol increases as due to the absorption of calcium from the gastrointestinal tract. Chart 4, case 805, represents a normal individual. His lung fields showed only a calcified tracheobronchial lymph node. In chart 4A, as in the case of all subsequent patients, the 4:00 P.M. determination was taken on the day preceding the experimentation. Chart 4A shows seven determinations from 8:00 A.M. to 8:00 A.M. with no intake except water. Chart 4B shows, in addition to water, 20 cc. of viosterol, which was given in 4-cc. doses at 8–10–12–2–4. Only two determinations, 11.7 mgm. at 2:00 P.M. and 12.1 mgm. at 8:00 A.M., were obtained that might be considered due to the addition of the drug. As long as the patient maintained a water intake or had a residue of food in the intestine, we would doubt this slight increase to be from bone in such a short period of time, or as long as the water contained calcium. In chart 4C we get from feeding milk alone an elevation of phosphorus and one elevation of calcium to 12.1 mgm. When activated ergosterol is added to the same

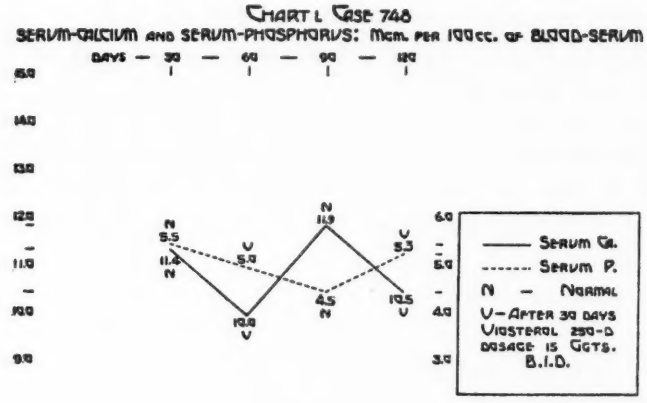

CHART 1

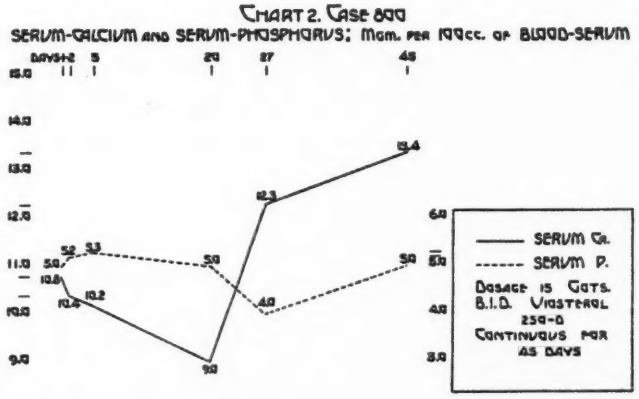

CHART 2

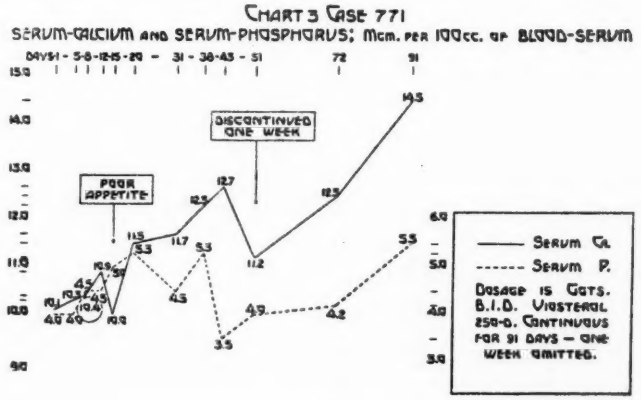

CHART 3

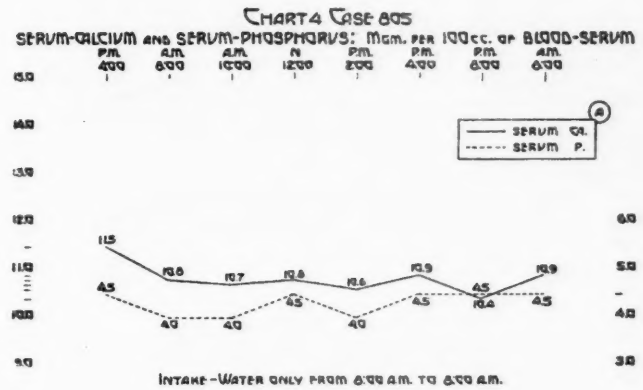

CHART 4a

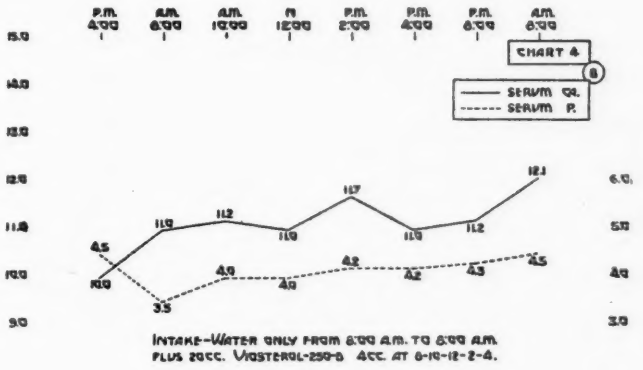

CHART 4b

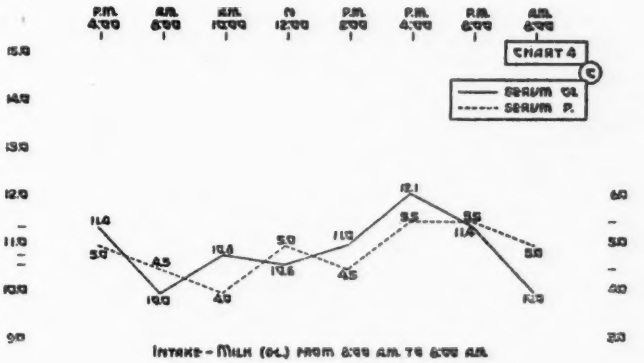

CHART 4c

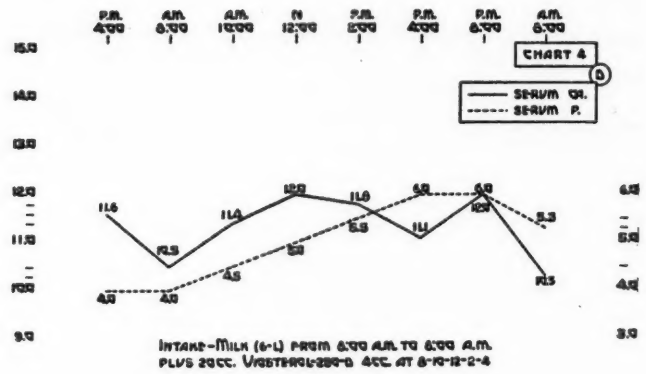

CHART 4d

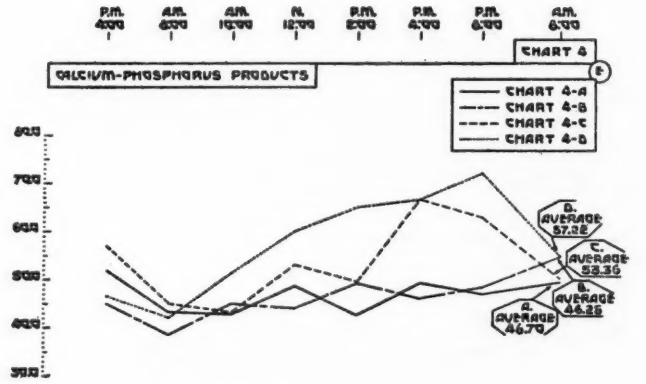

CHART 4e

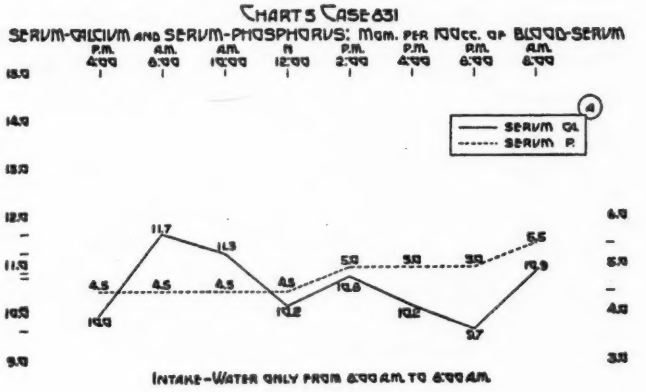
CHART 5 CASE 631
SERUM-CALCIUM AND SERUM-PHOSPHORUS: MGM. PER 100CC. OF BLOOD-SERUM
SERUM CA
SERUM P.
INTAKE-WATER ONLY FROM 6:00 A.M. TO 6:00 A.M.

CHART 5a

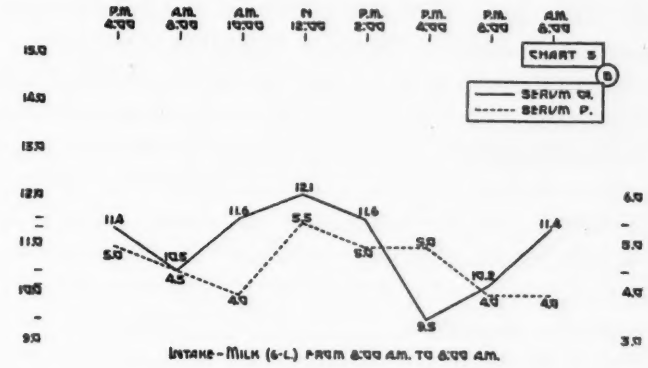

CHART 5b

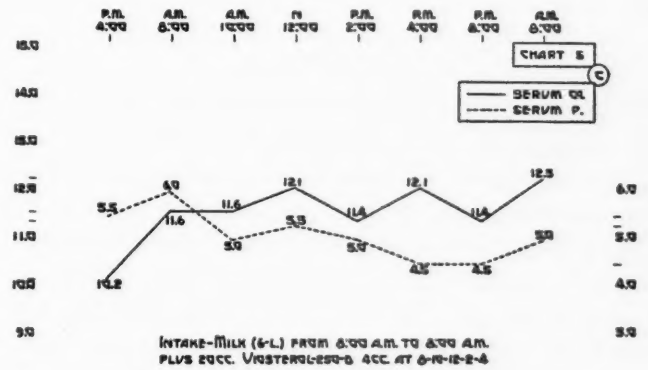

CHART 5c

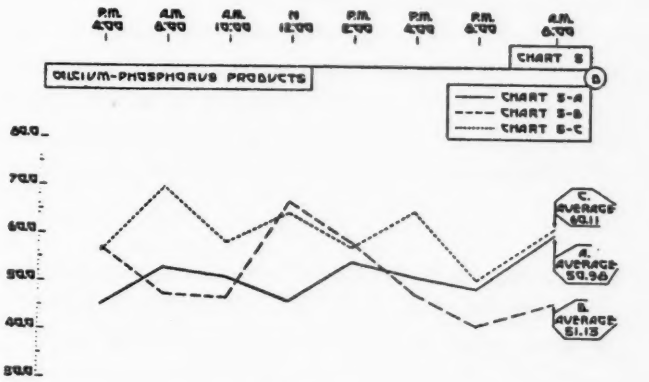

CHART 5d

diet of milk (61) a higher elevation of calcium and phosphorus occurred than obtained in chart 4D. The Ca × P product of these four observations compiled in chart 4E show a higher product with milk plus the drug.

Chart 5A, case 831, gives the normal determinations on a patient with far-advanced pulmonary tuberculosis. Chart 5B shows the patient on a diet of milk, and chart 5C shows the patient on a diet of milk and activated ergosterol. These two charts show that there is a similar tendency for the concentrations to increase if food is supplied with the drug. Chart 5D shows a Ca × P product of the three determinations. Even though the calcium-phosphorus concentrations were at a higher normal for that particular individual on that particular day a smoother and more sustained curve occurred with the milk plus activated ergosterol.

METHODS

Our determinations for calcium were made according to the Clark and Collip (33) method, and a modification of the method of Kramer and Tisdall (34). In order to diminish the quantity of blood used, which in turn lowers accuracy, LaMotte's (35) modification of the Roe and Kahn (36) method was used in part for phosphorus, but the method of Benedict and Theiss (37) was later adopted; however, we used 1 cc. of serum in both the method of Clark and Collip (33) and in the method of Benedict and Theiss (37). Phosphorus determinations are most difficult, since they must be determined within an hour after the specimen is obtained because of the decomposition of organic phosphorus. All determinations were run by the same technician to reduce the chance of experimental error. Comparative blood was taken at the same time of day. Many patients at times gave a higher concentration of either element after a night's rest. A much lower level is often reached during the day. If the drug was discontinued the determinations were made the same day.

CONCLUSIONS

1. Our experiments, so far, lead us to believe that activated ergosterol, 250 D, in the dosage of 15 drops, b.i.d., increases the absorption of calcium and inorganic phosphorus in the gastrointestinal tract.

2. On an ordinary normal hospital diet it takes approximately thirty days for this dosage to produce a sustained response with these elements in the blood-serum.

3. The concentration of calcium and phosphorus furnishes a check on

the symptoms of the patient during the feeding of activated ergosterol. If small elevations are obtained between the sixtieth and ninetieth day of administration, together with loss of appetite, the symptoms should be used as the guide in discontinuing the drug for a rest period.

4. The calcium concentration is more constant upon which the drug seems to have an accumulative effect.

5. The product, Ca × P, furnishes a more accurate criterion for proving the effect of activated ergosterol on the calcium and phosphorus in the blood-serum.

6. The maintenance of a higher concentration of calcium and phosphorus in the blood-serum below the point of toxicity produces no deleterious effect upon the healing of either acute or chronic pulmonary tuberculosis. In the end it may prove to be far more efficacious in the acute disease than sunshine is in chronic pulmonary tuberculosis.

Grateful acknowledgment and thanks are due Miss Grace Heimann of Boehne Hospital Laboratory for her accurate work on the blood-sera.

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TUBERCULOSIS IN ADOLESCENTS

A Study of 1000 School-Children in New York City Made under the Auspices of the Bellevue-Yorkville Health Demonstration in 1930[1]

MARGARET WITTER BARNARD, J. BURNS AMBERSON, JR., AND MARION FRANKLIN LOEW

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[1] The Bellevue-Yorkville Health Demonstration is one of three demonstrations in the State of New York financed by the Milbank Memorial Fund for the purpose of trying out in selected areas approved methods for the prevention of disease and the promotion of health with more generous appropriations than are ordinarily at the command of the public health authorities and private agencies. The area covered by the Bellevue-Yorkville Health Demonstration lies on the eastern side of Manhattan, between Fourteenth and Sixty-fourth Streets, extending west to Fourth Avenue below Forty-second and to Sixth Avenue above Forty-second Street. Its headquarters are the Bellevue-Yorkville Health Center, at 325 East Thirty-eighth Street. Active work was begun in January, 1927. In 1930, when the project which is the subject of this report was carried out, the Director of the Demonstration was Edward T. Devine, and the Chairman of the Board of Managers was Shirley W. Wynne, M.D., Dr.P.H., Commissioner of Health of the City of New York.

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I

THE PROJECT

As a special project in the spring of 1930 we undertook to examine a thousand 13-and-14-year-old children from the public and parochial schools in the Bellevue-Yorkville District, including in the examination X-rays of the chest.

There were two main reasons for undertaking this project. First, we wished to make a trial of method, to determine if possible what would be an effective way in a community like New York City to find or "screen out" those cases of tuberculosis in children which are generally assumed to be an important source of tuberculosis in young adults. For this reason we used personnel and methods which might be applicable to future use by the Department of Health.

Second, we wished to find out the kind and amount of tuberculous infection in a cross-section of our child population and to study the factors influencing its prevalence. For this reason we chose a group which, we could assume from the work of others, would give us our largest yield of cases among the children still subject to supervision by the Department of Health. In the 13-and-14-year-old group we could expect to discover some of the lesions of first infection often incurred in early childhood as well as some of the so called "adult type" of parenchymal lesions which, as McPhedran and others have shown, begin to appear between the tenth and the twelfth years of age.

It was arranged that this examination should take the place for these children of the routine examination by the school medical service of the Health Department. A "school stub" for each child, showing what defects were discovered, was given to the Health Department nurse in whose jurisdiction the child belonged, whereupon she became responsible for getting the defects corrected, just as if the examination had been made by the Health Department's medical squad. In the fall a letter was written to the parent or guardian of each child, reporting what the X-rays showed and reviewing the child's needs in other respects, and offering a second chest examination, with X-ray, when that was indicated. Carbon copies of these letters were sent to the school principals. For children who applied for working papers in June, 1930, a transcript of this examination was accepted by the Bureau of Child Hygiene in place of the regular examination.

A thousand was fixed upon as the number of records to be secured. This, it was thought, would be enough to make the study of value; and it was about as many examinations as the available space, equipment and personnel could be expected to handle.

It was hoped that the entire number could be secured from the schools in the Yorkville District of the Department of Health (that is, the territory between 34th and 64th Streets, east of Fourth Avenue below 42d Street and east of Sixth Avenue above 42d), as the make-up of its population is somewhat less complex than that of the Bellevue District (below 34th Street), and also because in the Yorkville District the nursing service of the Department of Health operates on a "generalized" system. The advantages of the generalized service were apparent in two ways: because of the flexibility of the system it was possible, even with a limited staff, to provide for the extra work more easily than with a specialized service; and the nurses, being better acquainted with the families in their territory, were themselves more interested, and were more successful in enlisting the interest of the parents.

A preliminary listing by the Department nurses indicated 1100 children of the desired age in the Yorkville District schools, but permission for the complete examination could be secured from the parents of only 766. To make up the rest of the number desired, children were taken from four schools below 34th Street, the majority from a junior high school for boys.

It was not feasible to keep strictly between the age lines of the thirteenth and fifteenth birthdays. The nurses were instructed to include all children who should have reached their thirteenth birthday on May 1, 1930, and should not yet have passed their fifteenth. Some who were younger or older got into the lists; and, as the examinations were spread over nearly four months (from early in February to late in May), some who were thirteen or fourteen on May 1 were twelve or fifteen when they were examined. Nine-tenths of the thousand included in the study, however, were within the desired age limits, and the rest were not far outside.

Altogether 1071 children were examined. The 71 records not included in this study were the 49 in which for some reason the tuberculin test was not completed and the 22 who were the furthest below thirteen or above fifteen years of age.

These thousand children, therefore, are not a "selected" group, except as permission for the tuberculin test and the composition of the population in this part of the city operated as selective factors. They are not

merely "a sample" of the children 13 and 14 years of age in this District, but are in fact two-thirds or three-fourths of all such children attending the public and parochial schools.

Because, however, of the differences in the composition of the population in different parts of New York, it cannot be assumed that our thousand children are typical of the 13- and 14-year-old public- and parochial-school children of the city. On the contrary, probably a thousand children from a similar area anywhere else in the city would differ considerably from our thousand as to race, nationality of parents and home conditions. In Harlem or on the lower East Side the contrast probably would be decided. That our findings would hold true for a group in which Negroes or Jews predominate is highly improbable. In New York the presumption is against assuming that any district is typical of the whole.

II

THE EXAMINATION

The examination included the following features:

1: A thorough general pediatrics examination, including tests of vision and hearing, and comparison of weight with standards for age and height. Actual time with the doctor averaged twelve minutes for each child. All the examinations were made by Dr. Loew, who also tabulated her findings.
2: Analysis of urine for albumin and sugar.
3: An intracutaneous (Mantoux) tuberculin test. The late Dr. Krumwiede, Assistant Director of the Health Department Laboratories, set aside for this project lot no. 85 of Old Tuberculin, and this was made up into special packages to facilitate the preparation of the two dilutions. A sample of tuberculin was submitted to Dr. Aronson of the Henry Phipps Institute, who, after using it in various ways, was of the opinion that it was comparable in strength to the tuberculin used at the Institute and would give comparable results. The tuberculin tests were administered and read by Dr. Barnard and Dr. Loew. The technique of injection and reading of the reactions was that used at the Henry Phipps Institute and described in the *Diagnostic Aids* of the National Tuberculosis Association.[2]

As it was considered impracticable to give three doses, an initial dose of 0.1 mgm. was given in the left arm at the time of the physical examination. The arms were read 48 hours later,—at school, to avoid asking the children to come

[2] *Childhood Type of Tuberculosis*, by Henry D. Chadwick and F. Maurice McPhedran. *Diagnostic Aids*, National Tuberculosis Association, 1930.

to the clinic a second time. Those who showed no reaction at this reading received a second injection (1.0 mgm. in the right arm) and their arms were again examined 48 hours later.

In no case was there any serious trouble with the arm, and minor sloughing occurred in only nine cases. We think therefore that for this age-group it is entirely safe to begin with 0.1 mgm. dose.

Some children who gave histories of previous tests were injected, and in a few other instances we repeated the tests after a short interval. In none of these cases was the reaction unduly severe. We therefore believe that, if it is difficult to obtain a reliable history of a previous tuberculin reaction, there is no danger to the child in repeating it.

4: X-rays of the chest. In most cases three films were taken: a stereoscopic pair and one left anterior oblique. The same technician took all the films and, although we experimented somewhat, a fairly stable technique was maintained. A 60-milliampere tungsten tube with a medium focus was used, and all the films were Eastman-duplitized-safety. The diameters of the chests were measured in inches with calipers and divided into two general groups: those under seven inches, and those seven inches and over. The milliamperes were kept constant at 100, while the distance, time, and K.V.P. were varied according to the measurement of the chest:

		Chest measurement less than seven inches	*Chest measurement seven inches and over*
Distance	Stereo	40 inches	50 inches
	Oblique	36 inches	36 inches
Time		$\frac{1}{15}$ second	$\frac{1}{10}$ second
Milliamperes		100	100
K.V.P. range		From 70 for $5\frac{1}{2}$ inches up to 78 for $6\frac{3}{4}$ inches	From 71 for 7 inches up to 91 for $10\frac{1}{2}$ inches

K.V.P. was increased 4 points for obliques, regardless of measurement.

The films were read independently by Dr. Barnard and Dr. Amberson. In the few cases in which their first interpretations differed, they reached agreement in conference.

5: A history was secured of the child's previous health,—the principal diseases, operations, accidents and preventive treatments,—and information about the present state of health of other members of the family and the cause of death of any members who had died, together with some general data about the economic and social status of the family. On these points the information given by the child or its mother at the time of the examination was supplemented and corrected by the nurse in at least one visit to the home.

III

PROCEDURE

The examinations were made in the clinic space of the Department of Health at the Bellevue-Yorkville Health Center. The Department of Health supplied the films, while the Demonstration met the expense of extra personnel,—a pediatrician to make the examinations, a nurse to have charge of the sessions and an assistant in the developing room. Aside from this, the work was done by the regular staff of the Department and the Demonstration.

A plan of procedure was worked out in consultation with the appropriate officials of the Department of Health, the Department of Education and the Catholic School Board. The schedule was arranged with a view to disturbing the school routine as little as possible.

Under the generalized nursing system operating in the Yorkville District one nurse is assigned to each school and its surrounding territory. Each of these nurses was made responsible for explaining the project at her school, making up her list of eligible children, and obtaining the parents' signatures on the consent cards. She also arranged for her group to be at the clinic at the appointed time. Afterward she made a visit to the home to explain the doctor's findings to the parents and was responsible for the follow-up work to correct the defects which were discovered.

Seventy-four clinics were held. They averaged three and one-half hours each, and 15 or 20 children were examined at each session.

As an intracutaneous tuberculin test was part of the examination it was considered advisable to have the consent of the parents in writing. For this purpose the following form was used on a 3 x 5 card:

CITY OF NEW YORK, DEPARTMENT OF HEALTH
PARENT'S CONSENT FOR EXAMINATION OF CHILD

.....1930

I, parent of.....
herewith grant permission for my child to have a complete health examination, including any necessary tests.

Signed.....

Address.....

This examination will be made at the Bellevue-Yorkville Health Center, 325 East 38th Street. Parents are urgently invited to be present.

The proportion of consents secured from the different schools seemed to be in direct proportion to the interest of principal, teachers and nurse. It seemed to us that mass psychology played a large part. If the test was presented to the children as a very desirable thing they were all eager to get their cards signed at home. On the other hand, the slightest opposition or even apathy on the part of those in charge was immediately reflected in a spirit of opposition among the children, who often influenced their parents not to sign. The number of true conscientious objectors among the parents was very small.

Seventy per cent of the eligible children in the Yorkville schools were examined: 61 per cent of those in the parochial schools and 78 per cent of those in the public schools. One of the larger parochial schools had

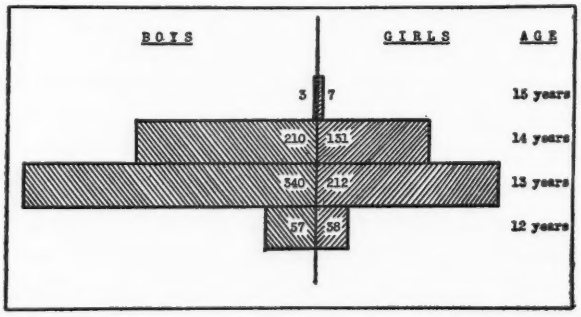

DIAGRAM 1. Sex and age of the 1000 children included in the study.

a record of 92 per cent examined, and one of the larger public schools a record of 90 per cent.

We believe it would not be impossible to require this test as a routine procedure in the schools, and that there would be no difficulty as soon as the parents became accustomed to it.

IV

THE CHILDREN AND THEIR HOMES

The group of a thousand children was made up of 612 boys and 388 girls. Their ages on the day of examination ranged from 12 years, 4 months, to 15 years, 2 months, with 13 years, 8 months, as the median and 89 per cent between the thirteenth and the fifteenth birthdays. (Diagram 1.)

All but a very few were born in the United States. Through their parents, however, they represented most of the countries of Europe and

North America, and also Argentina, Turkey, Armenia, China and Japan. There were no Negroes, and very few Jews compared with their proportion in the population of the whole city. Children of Italian parentage (36 per cent of the total) and of Irish parentage (15.6 per cent) constituted more than half of the group. (Diagram 2.)

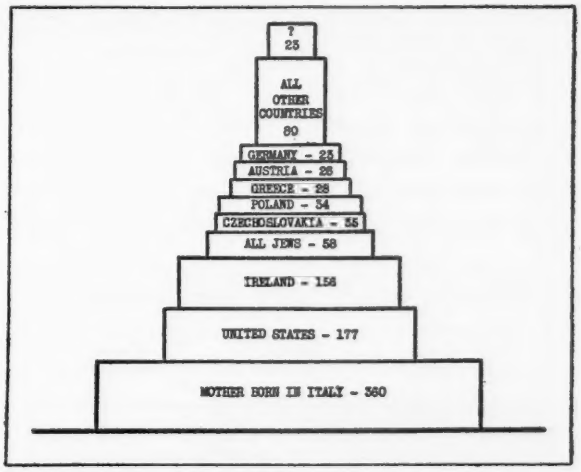

DIAGRAM 2. Race or nationality of the 1000 children. This classfication is based on birthplace of mother, except that all the Jews are grouped together, because in a study of tuberculosis their race is of more interest than their nationality. The relative size of the groups, as represented in the diagram, is proportional to the *area* of the superimposed blocks, not to the length of their base-lines.

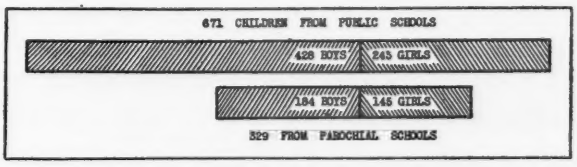

DIAGRAM 3. Distribution of the 1000 boys and girls between public and parochial schools.

About two-thirds of them came from the public schools of the District, one-third from the parochial schools. (Diagram 3.) They were scattered all the way from the ungraded classes up to the first years of High School. Ten per cent were below the sixth grade, which would indicate retardation for even the youngest of them.

Social and Economic Conditions

Two hundred of the children, exactly one out of five, had lost either father or mother or both, and in 23 other cases the parents were not living together.

As indicated by the occupation of father or step-father, there was a wide range in economic and social status: from laborers, construction workers, waiters, porters, small merchants, truckmen, and taxi-drivers, up to engineers and representatives of the professions.

At least a fourth of the mothers were working for wages away from home and others helped in the family store or earned money at home by janitor service, sewing, washing or keeping lodgers. Thirty-two of the thousand children were working for wages outside school hours or carrying responsibility for the cooking and housekeeping for the family.

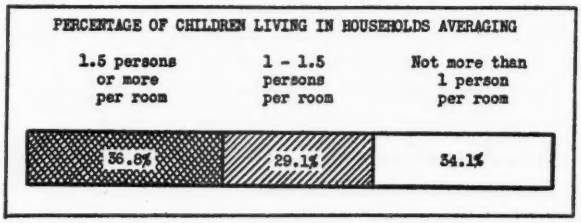
PERCENTAGE OF CHILDREN LIVING IN HOUSEHOLDS AVERAGING
1.5 persons or more per room
1 - 1.5 persons per room
Not more than 1 person per room
36.8%
29.1%
34.1%

DIAGRAM 4. Classification of the 1000 children according to degree of congestion in their homes.

Rents paid by these families ran from $10 for three rooms to $100 for eight and $125 for seven. More than half the families paid less than $30 a month; only 12 per cent paid $50 and over or owned their homes.

About half the families had a private toilet. The other half used a common toilet located in the hall or, in a few instances, in the yard or the cellar. A private bath was mentioned or implied in 20 per cent of the cases.

The homes ranged in size from two rooms to ten; the households from two persons to thirteen. The average was 4.5 rooms and 5.8 persons per household, which amounts to 1.3 persons per room. Five persons living in four rooms was the mode.

According to the old rule-of-thumb measure for overcrowding ($1\frac{1}{2}$ persons or more per room) 37 per cent of these children were living in "overcrowded" conditions. According to a more liberal standard of one person per room, 66 per cent were overcrowded. (Diagram 4.)

Very few of the families were known to be in receipt of a widow's pension or of assistance from a charitable organization. Over 60 per cent of them could give the name or address of a private physician whom they had consulted.

TABLE 1

Health history: number and percentage of children with record of certain diseases and treatments

DISEASE OR TREATMENT	NUMBER			PERCENTAGE		
	Boys	Girls	Total	Boys	Girls	Total
Total examined	612	388	1,000	100.0	100.0	100.0
Measles	307	277	584	50.2	71.4	58.4
Whooping-cough	149	177	326	24.3	45.6	32.6
Chickenpox	131	146	277	21.4	37.6	27.7
Mumps	96	70	166	15.7	18.0	16.6
Diphtheria	50	38	88	8.2	9.8	8.8
Scarlet fever	23	37	60	3.8	9.5	6.0
Pneumonias	55	43	98	9.0	11.1	9.8
Colds	532	329	861	86.9	85.0	86.1
Vaccination	605	385	990	98.9	99.2	99.0
Tonsillectomy	298	207	505	48.7	53.4	50.5
TAT or Schick test presumably negative	242	185	427	39.5	47.7	42.7

V

GENERAL HEALTH

History

The records of previous diseases, operations and treatments (table 1) in the lives of these children are probably fairly trustworthy, as such histories go. They were made by nurses accustomed to talking with these families and their neighbors about their children's health, familiar with the terms they use, and able to interpret them.

Of the 6 common contagious diseases of childhood, 1501 cases were recorded, an average of 1.5 per child. All six had occurred more frequently among the girls than among the boys, and the average was 1.24 cases per boy and 1.92 cases per girl. One in ten of the thousand had had pneumonia, some of them two or three times and one seven times. Eighty (64 boys and 16 girls) had had bones broken or had been injured in other ways through accidents. There were scattering instances of conditions requiring surgical treatment and of a great variety of diseases.

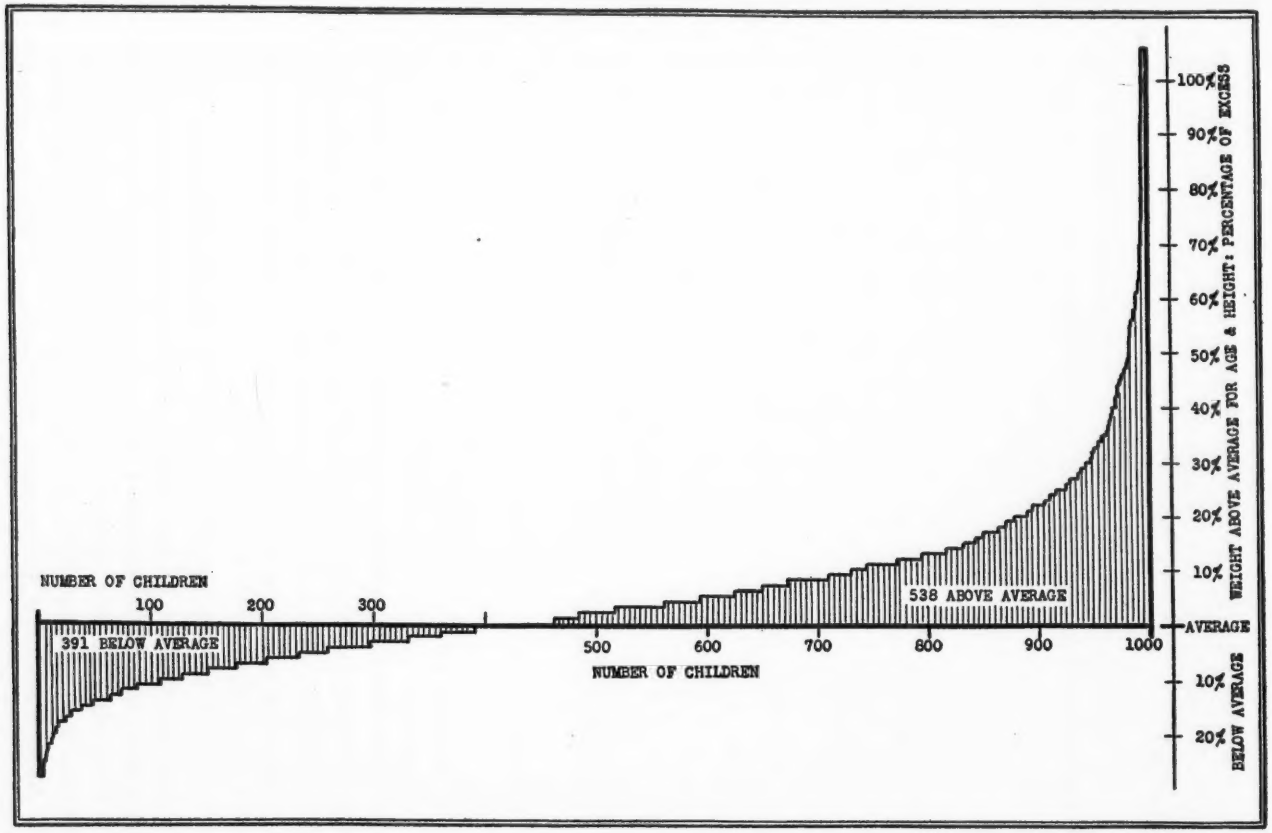

DIAGRAM 5. Weight of the 1000 children compared with average weight for age and height. The diagram represents the 1000 children ranged in a long row according to their deviation from the average weight: beginning at the left with the one furthest below average (28 per cent), progressing step by step up to the 72 who were just at the average, and then on up to the one furthest above average (106 per cent) at the right-hand end of the figure.

Colds or sore throats were admitted by 861 of the thousand, and 235 described them as "frequent."

All but ten of the thousand children had been vaccinated against smallpox. Just over half of them had had their tonsils, and in most cases also their adenoids, taken out. Over 40 per cent had received three injections of toxin-antitoxin or had had a Schick test which presumably was negative. All three of these prophylactic measures, especially immunization against diphtheria, were more frequent among the girls than among the boys.

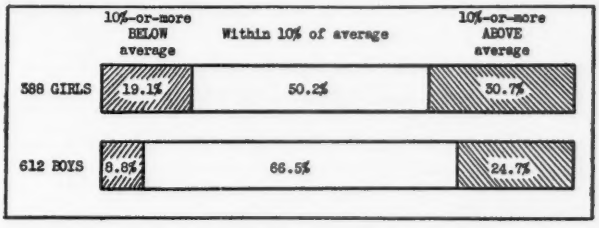

DIAGRAM 6. Deviation from average weight: by sex.

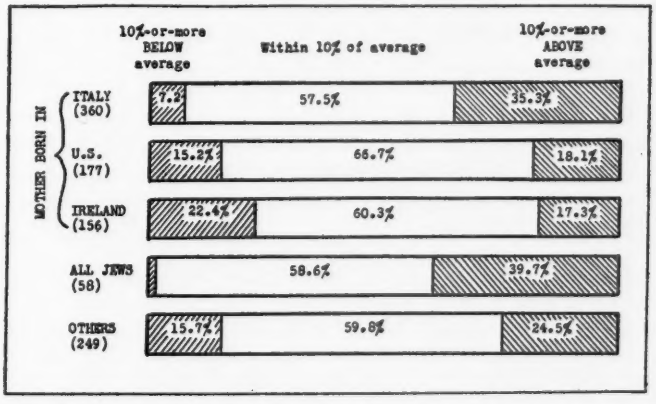

DIAGRAM 7. Deviation from average weight: by race or birthplace of mother.

Weight

Overweight was more conspicuous among these children than underweight. (Diagram 5.) Comparing the weight of each one with the average for healthy children of the same age and height as presented in the Baldwin-Wood tables, we found that 234 of the thousand were within 5 per cent of the average on one side or the other, 602 within 10 per cent; that 128 were 10 per cent or more below the average and 14 were 20 per

cent or more below, while 270 were 10 per cent or more above the average. The extremes were a boy of Irish parentage 28 per cent below and a girl of Italian parentage 106 per cent above.

There was more deviation in both directions from the average among the girls than among the boys (diagram 6); and there were very important differences in this respect according to race and nationality (diagram 7).

The Physical Examination

It was not expected that the general examination would reveal the cases of tuberculous disease, but it was essential as an aid in evaluating

TABLE 2

Principal defects found in the 1000 children

Poor posture	537
Carious teeth (2x and 3x)	528
Flat foot	363
Poor nutrition (3 and 4)	246
Tonsils (3 and 4)	231
Diseased pharynx or suspected sinusitis	209
Vision defective and not corrected by proper glasses	173
Lymph nodes palpable or enlarged (cervical: 116)	141
Defective breathing	127
Heart	63
Organic disease, actual or suspected	52
Functional disorder	11
Skin diseases (exclusive of acne and other minor affections)	53
Nervous disorders	51
Eye condition	51
Defective hearing	40
Ear condition	34
Lungs: abnormal physical signs (see page 625)	24

the findings from the tuberculin test and the X-ray. What it did reveal was an appalling number of defects in a group of children who were in sufficiently good health to be attending school regularly.

More or less serious defects were found in all but 27 of the thousand children. The defects found in large numbers are listed in table 2, following in a general way the classification used by the medical school-inspection service of the Department of Health, and arranged in order of frequency of occurrence.

On the basis of the pediatrics examination a "health grade" was given to each child. The following plan of grading was used:

A: No defects
B: No defects requiring other than ordinary attention from home and school
C: Minor defects requiring special attention
D: Serious defects needing special medial care

Only 27 of the entire thousand could be graded *A*, while 168 were *D*. The total in good general condition (*A* or *B*) was just about one-fourth of all. (Diagram 8.)

The 227 children graded *B* had such minor defects as unclean teeth, small cavities in one or two teeth, poor posture or flat arches. They are the children who with just a little more care could easily be in perfect physical condition.

Grade C was by far the largest group, including over half the total. These children had one or more defects requiring special attention, frequently in addition to one or more minor defects such as are found in

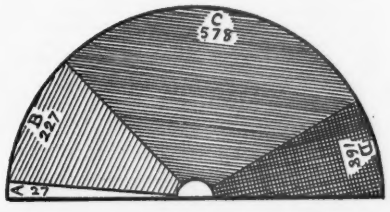

DIAGRAM 8. Classification of the 1000 children as to general health.

grade B. Of the 578 in grade C, 330 had only one "C-grade" defect; the others had two or more, up to five in one case. The defects which were considered sufficient to put a child in grade C were as follows:

1: Poor Nutrition: Children classed "3" or "4" as to nutrition were graded *C*, whether or not they had other defects. In deciding on nutrition, muscle tone and skin turgor were taken into account as well as weight, and the group includes a few children who were of average weight or slightly above the average for their age and height according to the Baldwin-Wood tables.
2: Carious Teeth: Over half the children had carious teeth. Among these were many who had numerous cavities or badly decayed teeth, or infected gums, so urgently requiring care that this condition alone was enough to make the child grade C.
3: Diseased or Hypertrophied Tonsils: According to the classification used by the medical school-inspection service of the Department of Health, 231 children had tonsils which required attention and the opinion of a nose-and-throat spe-

cialist as to their removal. One had such badly diseased tonsils that they were enough to put him in grade D. The others, unless they had other defects of a more serious nature, were graded *C*.

4: Defects of Vision: Every child's vision was tested by means of the Snellin *Test Chart*, with glasses as well as without, in the case of those who had glasses. A vision of 20/40 or over, not properly corrected by the glasses the child was wearing, was considered enough to put him in grade C.

5: Defects in Hearing: Deafness in children is a serious defect which should have definite care. Those who showed any defect in hearing, therefore, however slight, were classed as grade C if only one ear was affected, while deafness in both ears relegated the child to grade D.

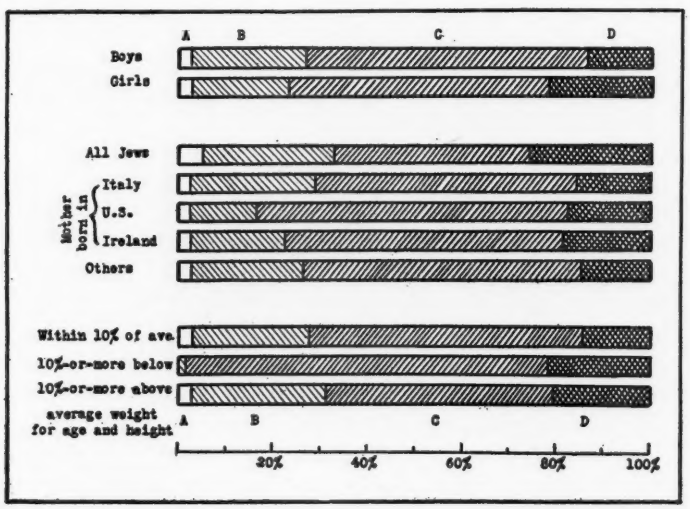

DIAGRAM 9. Health grades: by sex; by race or birthplace of mother; and by deviation from average weight.

6: Skin Lesion: Any skin lesion other than simple acne was deemed sufficiently important to place the child in grade C. In many cases there was a combination of ringworm and scabies or ringworm and impetigo, and one child had all three.

7: Urinalysis: Every child whose urine showed sugar (12 cases) or albumin (95 cases) was placed in grade C because of the importance of a proper check-up.

The 168 children (one out of six) who were graded *D* were all considered to be in need of definite medical care. Most of them had more than one defect requiring observation or care, but certain conditions were deemed sufficiently important in themselves to demand a *D* grade.

Among the serious conditions any one of which put a child in grade D were the following:

1: Organic heart disease, actual or suspected, of which there were 52 cases.
2: Conditions warranting presumption of sinusitis: postnasal drip, definite tenderness over the maxillary antra or frontal or ethmoidal sinuses, headache, or an obstruction in the nasal passage.
3: Positive signs in the lungs, found in 24 cases, only six of which conformed in any way to the X-ray findings.
4: Glandular dyscrasias, such as are usually to be found in a group of adolescents.

There were 24 cases of enlargement of the thyroid, many accompanied by one or more of the triad of symptoms,—rapid pulse, lowered nutrition, mild tremor of the hands. While many of these cases may be due to the physiological changes of puberty, it was considered advisable to refer them for basal-metabolism tests to determine the degree of overactivity.

Overweight amounting to 50 per cent, or more above average for age and height, of which there were 21 cases, was considered presumptive evidence of some pathological condition. Five of the boys in this group showed an almost entire absence of secondary sexual characteristics, and were suspected of a pituitary dyscrasia (Frölich's syndrome).
5: Various conditions occurring in smaller numbers, including deafness in both ears, marked anaemia, vaginitis, suspected congenital syphilis, extreme postural defects, and a few acute conditions such as sore throat with elevated temperature, and bloody diarrhoea.

The girls had a noticeably higher proportion in grade D than the boys, 21.9 per cent compared with 13.6 per cent (diagram 9), and a smaller proportion in both grade B and grade C.

Comparing the four principal population groups (diagram 9), the Jews had the highest proportion in both grade A and grade B (32.8 per cent together), and also at the other end, in grade D (25.8 per cent). The Italians came next in the proportion graded *A* and *B* (29.2 per cent) and had the lowest proportion graded *D* (15.8 per cent). The children of native parentage had the smallest proportion of all in good health as represented by grades A and B (16.4 per cent) and the largest group of all in grade C (66.1 per cent). The Irish presented a somewhat similar distribution (22.6 per cent in grades A and B, 59.0 per cent in grade C).

Comparing the three weight-groups (also on diagram 9), 14.1 per cent of the children who were within 10 per cent of the average weight for their age and height were in grade D; 21.9 per cent of those 10 per cent or more

below average; and 20.4 per cent, almost as large a proportion, of those 10 per cent or more above average. Grade C of the underweight group was so large (76.5 per cent of the group) because all children 10 per cent or more below average weight were graded *C* unless their general condition was so good in other respects as to overbalance this presumptive evidence of poor nutrition.

VI

THE TUBERCULIN TEST

A positive skin reaction to tuberculin will occur in an individual who has been infected with tubercle bacilli unless the infection has completely

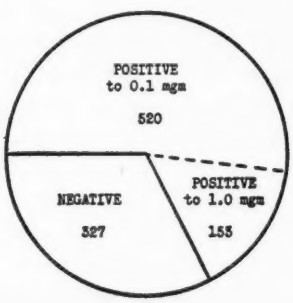

DIAGRAM 10. Classification of the 1000 children as to tuberculin reaction.

healed or unless an acute febrile condition interferes with the reaction. The latter possibility is excluded in this group, and we may therefore assume that the group that reacted to tuberculin included all with significant tuberculous infection.

Five hundred and twenty of the thousand children showed a reaction to the first injection of tuberculin (0.1 mgm.) on a reading 48 hours after it was administered. One hundred and fifty-three more reacted to the second dose (1.0 mgm.) making a total of 673 reactors or 67.3 per cent. (Diagram 10.)

As to intensity of reaction they were classified as follows:

Reactors to 0.1-mgm. dose	
++++	9
+++	268
++	146
+	96
?+	1

Reactors to 1.0-mgm. dose	
+++	3
++	16
+	95
? +	39

Those with a questionable reaction do not include any in which there was redness only, which might have resulted from the phenol in the saline solution. They are the ones which showed a slight or questionable oedema, and it has therefore seemed proper to include them among the reactors.

Even in a limited area such as that used for this project there are conspicuous differences between schools as to amount of infection. (Diagram 11.) These differences may be due to many factors, of which the racial composition of the groups undoubtedly is an important one. They serve to emphasize the necessity of great care in interpreting any figures of incidence of infection which are derived from limited sources.

Among the boys the proportion of positive reactions, especially to the second dose, was slightly greater than it was among the girls. (Diagram 12.)

Comparing the positive and negative groups by age (table 3) we find a slight difference and a trend which is in accord with the general belief that the incidence of tuberculous infection increases steadily with each year of age. The percentage of positives is higher among the 13-year-olds than among the 12-year-olds, and higher still among the 14-year-olds. The number of 15-year-olds is too small to be of any significance.

If we consider the three groups whose mothers were born in Italy, the United States and Ireland, and who together constitute two-thirds of our entire group, and the group of Jews, which is next in size, we find that there is distinctly more infection among those of Irish parentage and among the Jews than in the other two groups. (Diagram 13.) The predominance of Italians among our thousand cases, with their lower incidence of infection, therefore affects our general findings, and may be a reason why our percentage of positive reactions was lower than that found by Opie in Philadelphia.

We are accustomed to think of overcrowding as one of the important factors in the spread of tuberculous infection. It may therefore be surprising that there is little evidence of its importance (table 4) among our thousand children. The percentage of positives was practically the same at all three degrees of congestion.

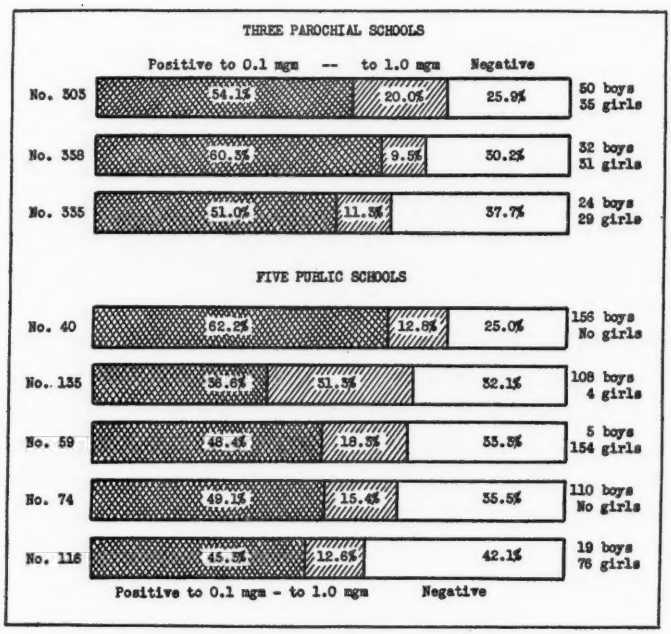

DIAGRAM 11. Tuberculin reaction: by schools.

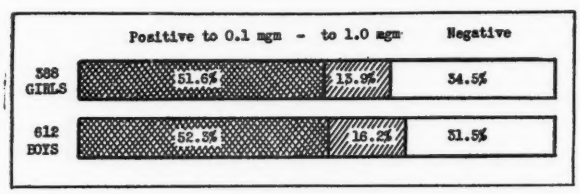

DIAGRAM 12. Tuberculin reaction: by sex.

TABLE 3

Tuberculin reaction: by age

AGE	TOTAL EXAMINED	NUMBER		PERCENTAGE POSITIVE
		Positive	Negative	
years				
15	10	5	5	50.0
14	341	240	101	70.4
13	552	368	184	66.7
12	97	60	37	61.9
Total.....	1,000	673	327	67.3

Another index to living conditions is the rent paid, and here again (table 5) we find no significant difference. The percentage of positives in the lowest rental group was only a very little higher than in the other two.

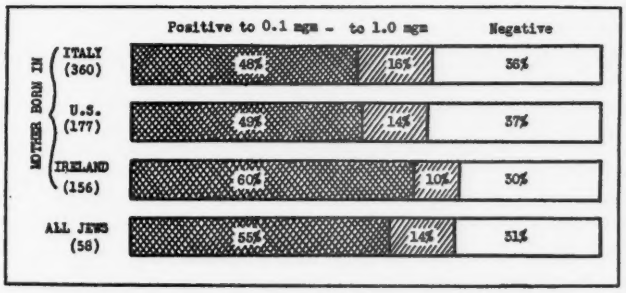

DIAGRAM 13. Tuberculin reaction: by race or birthplace of mother.

TABLE 4

Tuberculin reaction: by housing conditions

PERSONS PER ROOM	TOTAL EXAMINED	NUMBER		PERCENTAGE POSITIVE
		Positive	Negative	
1½ or more	350	234	116	66.9
1–1½	277	190	87	68.6
1 or less	324	212	112	65.4
Information lacking	49	37	12	75.5
Total	1,000	673	327	67.3

TABLE 5

Tuberculin reaction: by amount of rent paid

RENTAL	TOTAL EXAMINED	NUMBER		PERCENTAGE POSITIVE
		Positive	Negative	
Under $30 (including paid by service)	449	309	140	68.8
$30–$50	273	182	91	66.7
$50 and over (including house owned)	102	67	35	66.7
Total for which information was given	824	558	266	67.7

Although it is commonly assumed that certain diseases predispose toward tuberculosis, there has been little real evidence for or against this view. It is therefore interesting to note the differences between positive and negative tuberculins with reference to the history of certain common

diseases. The significance of these differences is not clear, but they suggest that further study of this problem might be of interest.

Since a complete physical examination can be made available for most children, it is of great interest to see whether such examinations would afford us any clues as to the incidence of tuberculous infection. We see (table 7) that, as would be expected, a somewhat higher proportion of the negatives were in good general health than of the positives, 29.6 per cent

TABLE 6

Incidence of certain common diseases of childhood: by tuberculin reaction

DISEASE	PERCENTAGE WITH HISTORY OF SPECIFIED DISEASE		
	Of total examined	Of the 673 positive to tuberculin	Of the 327 negative to tuberculin
Measles	58.4	59.1	56.9
Whooping-cough	32.6	30.6	36.7
Chickenpox	27.7	26.9	29.4
Mumps	16.6	17.4	15.0
Diphtheria	8.8	8.6	8.0
Scarlet fever	6.0	6.5	4.9
Colds	86.1	86.5	85.0
Pneumonia	19.8	9.5	10.4

TABLE 7

Tuberculin reaction: by health grades

HEALTH GRADE	TOTAL EXAMINED	NUMBER		PERCENTAGE	
		Positive	Negative	Positive	Negative
A	27	19	8	2.8	2.4
B	227	138	89	20.5	27.2
C	578	392	186	58.3	56.9
D	168	124	44	18.4	13.5
Total	1,000	673	327	100.0	100.0

of the negatives falling in grades A and B, compared with 23.3 per cent of the positives.

If, now, we had divided our group into two large divisions,—those in good health (grades A and B) and those in poor health (grades C and D), and had applied the tuberculin test only to the latter, we would have screened out in this way 516 positives, or 76.7 per cent of our total number of positives in the thousand children. At first it would seem that this

would have been a fairly effective screen, but we have no clue as to the relative importance of the infection in the 23.3 per cent who would not have been found. To ignore almost a quarter of the entire amount of tuberculous infection does not seem a safe procedure.

TABLE 8

Tuberculin reaction: by deviation from average weight for age and height

DEVIATION FROM AVERAGE WEIGHT FOR AGE AND HEIGHT	TOTAL EXAMINED	POSITIVE TO TUBERCULIN	NEGATIVE TO TUBERCULIN
Below average			
20% or more	14	11	3
15%–19%	34	19	15
10%–14%	80	52	28
5%–9%%	132	89	43
Less than 5%	131	90	41
Average	71	46	25
Above average			
Less than 5%	132	90	42
5%–9%	136	100	36
10%–14%	101	66	35
15%–19%	48	35	13
20%–24%	38	23	15
25%–29%	26	17	9
30% or more	57	35	22
Total	1,000	673	327
Summary			
Below by 10% or more — Number	128	82	46
Below by 10% or more — per cent	12.8	12.2	14.1
Within 10% — Number	602	415	187
Within 10% — Per cent	60.2	61.7	57.2
Above by 10% or more — Number	270	176	94
Above by 10% or more — Per cent	27.0	26.1	28.7
Total — Number	1,000	673	327
Total — Per cent	100.0	100.0	100.0

In recent years pediatricians have rejected weight as a very valuable factor by itself in evaluating the general health of a child, but it is nevertheless important to see whether it would offer any criterion for separating those infected with tuberculosis from those not infected.

The only comparison which can be made is with the average weight

for age and height of American children. (Table 8.) This introduces a large element of error in comparing groups of different racial stock, but there are no standard tables of weight by race and nationality available.

From table 8 it appears that if we had selected for the tuberculin test only those of our thousand children who were 10 per cent or more underweight, as is frequently recommended, we would have discovered only 12.2 per cent of those who were actually infected with tuberculosis; and that there was even a slightly higher percentage 10 per cent or more underweight among the negatives than among the positives. Looking at the facts in another way (diagram 14), the group 10 per cent or more below average had a higher proportion of negatives than the group within 10 per cent or the group 10 per cent or more above average.

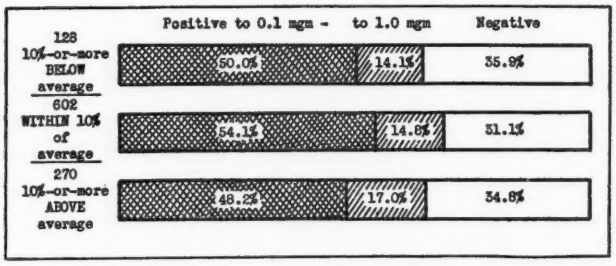

DIAGRAM 14. Tuberculin reaction: by deviation from average weight.

These findings may be due in some degree to the predominance of Italians in the group, but they agree in general with the opinion of others that tuberculous infection may be present in children who are of normal weight or above normal.

It is generally believed that the incidence of tuberculous infection is higher among children exposed to household contact with a case of pulmonary tuberculosis than among those who are not so exposed. Our findings agree with this: 85.7 per cent of those living in contact with a known case were positive compared with 67.3 per cent of the entire thousand. Putting it another way, however, the known cases of pulmonary tuberculosis in the families may be assumed to account for the infection in 30 cases, or one out of 22. On the other hand, five children known to have been exposed to infection in their homes had apparently not yet acquired it.

If we include the 64 *probable* cases of pulmonary tuberculosis in these families with the 35 *known* cases, we find a total of 99 of the thousand children who had been, or probably had been, exposed to the infection in their homes, of whom 69.7 per cent were positive to tuberculin. The entire 99, however, account for only 69 of the 673 positive tuberculins; and it is noticeable that the percentage of positives among the children in contact with a *probable* case is smaller than among those with no history of contact at all.

No doubt a complete and accurate history of current or recent exposure at home would disclose a probable source for many more. It is hardly conceivable, however, that even a complete list would come very near to accounting for the entire 673. The figures suggest that in New York City opportunities for infection outside the home, even for school-children, may be more important than has been generally realized.

TABLE 9

Tuberculin reaction: by exposure to household contact

EXPOSURE IN HOME	TOTAL EXAMINED	NUMBER		PERCENTAGE POSITIVE
		Positive	Negative	
To known case	35	30	5	85.7
To probable case	64	39	25	60.9
Total to known or probable case	99	69	30	69.7
All others	901	604	297	67.0
Total examined	1,000	673	327	67.3

Summary

Comparing the 673 children who reacted either to the first or to the second injection with the 327 who remained negative to both injections, the information at our command (see table 10) reveals comparatively little difference between the two groups as to composition and economic conditions. The positive group

1: Contained a somewhat larger proportion of boys than the negative group, a somewhat smaller percentage of Italians and a somewhat larger percentage of Irish;

2: Was a little older on the average,—about a month;

3: Had a somewhat smaller proportion 10 per cent or more above average weight for age and height, but also a smaller proportion 10 per cent or more below average;

4: Lived in households and apartments of practically the same size, paid a trifle less rent, and had the same proportion living in "overcrowded" conditions;
5: Had a history of about the same incidence of the contagious diseases of childhood, taken as a group, but somewhat less whooping-cough and a little more measles;
6: Were subject to colds in about the same proportion; and

TABLE 10

Comparison of children positive to tuberculin with children negative to tuberculin

ITEMS	POSITIVE	NEGATIVE
Total number of cases	673	327
Boys: percentage of total	62.3	59.0
Average age: years	13.74	13.66
Mothers born in Italy: percentage	34.5	39.1
Mothers born in Ireland: percentage	16.2	14.4
Weight 10% or more below average: percentage	12.2	14.1
Weight 10% or more above average: percentage	26.2	28.7
Average size of household: persons	5.8	5.7
Average size of home: rooms	4.5	4.4
Living in households averaging 1½ persons or more per room: percentage	36.8	36.8
Rent less than $30 per month: percentage	55.4	52.6
Contagious diseases of childhood: average cases recorded per child	1.50	1.51
Measles mentioned in history: percentage	59.1	56.9
Whooping-cough mentioned in history: percentage	30.6	36.7
Subject to colds: percentage	86.5	85.3
Tonsils removed: percentage	50.8	49.8
Graded *C* or *D* on general examination: percentage	76.7	70.0
In household contact with pulmonary tuberculosis:		
With a known case: Number of children	30	5
With a known case: Ratio to all children	1:22	1:65
With a known or a probable case: Number of children	69	30
With a known or a probable case: Ratio to all children	1:10	1:11

7: Had a somewhat larger proportion graded *C* or *D* on their general medical examination.

On the point of household contact with pulmonary tuberculosis, the ratio of children living in household contact with a verified case was much higher in the positive group than in the negative group (though very low in both), but the ratio of those in contact with the verified cases *plus* all probable cases was about the same in both groups.

VII

LESIONS DEMONSTRABLE BY X-RAY

Since the pulmonary and tracheobronchial lesions are in most cases difficult or impossible to demonstrate, the technical quality of the roentgenographs is of prime importance. Our technique of exposure is described on page 598. This, of course, does not have the high degree of efficiency of the procedure which has been tried by McPhedran in order to eliminate the illusions resulting from the motion of the heart and blood-vessels. As yet, however, it is not practical to adopt this rather complex technique in the average clinic. Generally speaking, our films were of a better quality than are ordinarily obtained in routine work. We feel, therefore, that they suffice for one of our chief purposes: namely, the practical test of a method which could be carried out in any well-organized and well-equipped clinic.

In respect to criteria of interpretation of chest X-rays of children, we are in close agreement with most others who have had experience in this work. One of the most severe demands on one's judgment is the differentiation of shadows of blood-vessels from those of actual tuberculous nodules. Here we tried to be conservative, considering a given density insignificant unless its character definitely labelled it otherwise. As a matter of convenience in considering the findings from the X-ray viewpoint alone, we grouped the lesions into two main classes, namely, apparently healed and clinically important.

In 171 cases with positive tuberculin reactions and in 13 cases which did not react, making a total of 184, there were tuberculous lesions demonstrable by X-ray. Of these, 71 were classed as apparently healed and 113 as clinically important. (Diagram 15.) In 26 cases evidence of the disease was found in the pulmonary parenchyma only; in 89 in the tracheobronchial region (lymph nodes) only; and in 69 in both situations.

Those classed as apparently healed were cases in which the lesions seemed to be reasonably well healed by fibrosis and calcification, so far as these were visible. A lesion was classed as clinically important if the calcified areas were extensive, or if they seemed to be of irregular density so as to suggest caseation and incomplete fibrosis and calcification, or if there was any obvious parenchymal infiltration which was recent or not completely fibrosed.

Very little is definitely known about the relation between intensity of tuberculin reaction and the character of the tuberculous lesions. If we

distribute the clinically important and apparently healed lesions by the intensity of reaction (table 11 and diagram 16), we see that in the negative group there were eleven demonstrable lesions, all apparently healed. In the group reacting to 1.0 mgm. of tuberculin (but not to 0.1 mgm.), lesions were present in 27, 14 of which, approximately one-half, were clinically important. In the group reacting to 0.1 mgm., lesions were present in 146, of which 99, over two-thirds, were clinically important.

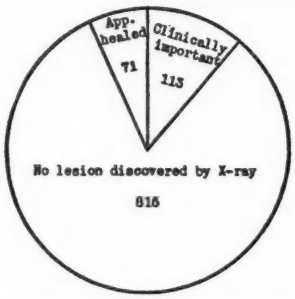

DIAGRAM 15. Classification of the 1000 children as to lesions demonstrable by X-ray.

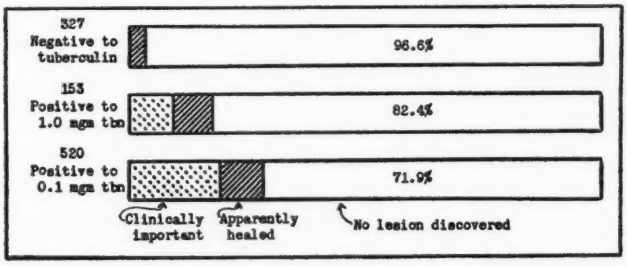

DIAGRAM 16. Demonstrable lesions: by tuberculin reaction.

This suggests that the extent and state of healing of lesions may have a direct correlation with the intensity of the tuberculin reaction.

We have seen (diagram 12) that the boys have a slightly greater incidence of tuberculous infection as evidenced by their tuberculin reactions. We now find (table 12) a similar difference in the number of cases with lesions demonstrable by X-ray.

There is a higher percentage of lesions among the boys, and of these lesions a larger proportion fall in the class of clinically important. These differences are slight and may be of doubtful statistical significance, but

TABLE 11

Lesions demonstrable by X-ray: by intensity of tuberculin reaction

TUBERCULIN REACTION	CHILDREN EXAMINED	CHILDREN WITH LESIONS		
		Total	Clinically important	Apparently healed
Negative	327	11	0	11
Positive to 1.0	153	27	14	13
?+	39	4	2	2
+	95	22	11	11
++	16	1	1	0
+++	3	0	0	0
Positive to 0.1	520	146	99	47
?+	1	0	0	0
+	96	9	5	4
++	146	36	25	11
+++	268	97	68	29
++++	9	4	1	3
Total	673	184	113	71

TABLE 12

Cases with lesions demonstrable by X-ray; by sex

LESIONS	TOTAL EXAMINED	NUMBER		PERCENTAGE	
		Boys	Girls	Boys	Girls
Clinically important	113	76	37	62.8	58.7
Apparently healed	71	45	26	37.2	41.3
Total with lesions	184	121	63	100.0	100.0
Total examined	1,000	612	388		
Percentage with lesions	18.4	19.4	16.2		

TABLE 13

Lesions demonstrable by X-ray: by age

AGE	CHILDREN WITH LESIONS			CHILDREN EXAMINED	
	Clinically important	Apparently healed	Total	Total number	Percentage with lesions
years					
15	1	0	1	10	10.0
14	37	25	62	341	18.2
13	68	38	106	552	19.2
12	7	8	15	97	18.6
Total	113	71	184	1,000	18.4

they suggest that it might be worth while to study this question further in other groups.

Comparing the distribution of lesions by age (table 13), we find that, except in the 15-year-old group, which is too small to be regarded at all, the incidence is practically the same. That is, the number of lesions discovered in the 12-year-old, the 13-year-old, and the 14-year-old groups has just about the same relation in all three groups to the number of children examined.

TABLE 14

Lesions demonstrable by X-ray: by health grades

HEALTH GRADE	CHILDREN POSITIVE TO TUBERCULIN	CHILDREN WITH LESIONS			CHILDREN EXAMINED	
		Clinically important	Apparently healed	Total	Total number	Percentage with lesions
A	19	0	3	3	27	11.1
B	138	22	14	36	227	15.9
C	392	74	46	120	578	20.8
D	124	17	8	25	168	14.9
Total.....	673	113	71	184	1,000	18.4

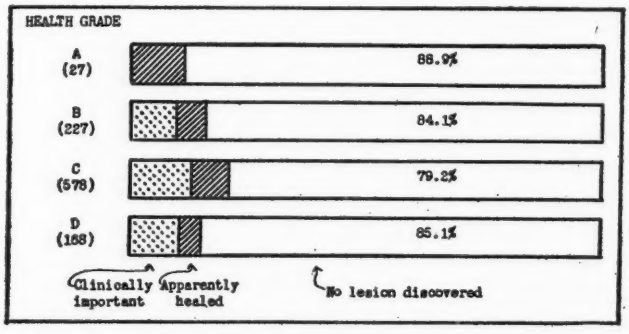

DIAGRAM 17. Demonstrable lesions: by general health.

It is of great importance to attempt to find what influence is exerted on the general health of children by tuberculous lesions of varying character, and for this information we must depend mostly on the X-ray findings. We found that 23.3 per cent of all the positive reactions to tuberculin occurred among the 254 children (25.4 per cent of the total) who were graded *A* or *B* on general health. We now see (table 14) that among these 254 children there were 39 who had demonstrable lesions (21.2 per

cent of all with lesions), of which 22 were clinically important and 17 were apparently healed. If we had omitted from the X-ray examination the children in good general health, we would have missed 22 out of the total 113 clinically important cases, or nearly 20 per cent.

The highest percentage of lesions was found in grade C. The percentage in grade B was a little higher than the percentage in grade D. (Diagram 17.)

TABLE 15

Lesions demonstrable by X-ray: by weight

WEIGHT	CHILDREN WITH LESIONS			CHILDREN EXAMINED	
	Clinically important	Apparently healed	Total	Total number	Percentage with lesions
10% or more below average	17	1	18	128	14.1
Within 10% of average	73	47	120	602	19.9
10% or more above average	23	23	46	270	17.0
Total	113	71	184	1,000	18.4

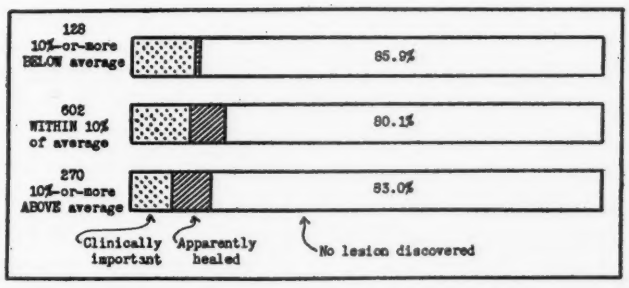

DIAGRAM 18. Demonstrable lesions: by deviation from average weight.

A study of table 14 does not permit any clear-cut deductions, save that the type of tuberculosis discovered in this group does not seem to be reflected in any way in the general health of the children.

Looking at the three weight-groups for incidence of demonstrable lesions (table 15 and diagram 18), it appears that the smallest percentage of lesions was found in the group 10 per cent or more below average weight for age and height, but in only one of these cases was the lesion apparently healed. The highest percentage was found in the group that was within 10 per cent of average weight. If we had selected for X-ray

the group 10 per cent or more below average weight we would have discovered only 17 out of the total 113 clinically important lesions, and only one apparently healed lesion out of the total 71 (table 15). Thus we would have missed approximately 90 per cent of the lesions demonstrable by X-ray in the entire thousand.

Among the 35 children with a history of household contact to a known case of tuberculosis, eight showed lesions on X-ray. Among the 64 who had probable history of contact, nine had lesions. In other words, 91 per cent of the children with lesions demonstrable by X-ray had no history of any known exposure to tuberculosis.

Summary

If we had X-rayed only the 673 who had a positive reaction to the tuberculin test, we would have discovered 173 of the 184 with tuberculous pulmonary lesions demonstrable by X-ray,—all but eleven.

If we had X-rayed only the 168 who were graded *D* on general health, we would have discovered 25 of the 184.

If we had X-rayed only the 128 who were 10 per cent or more below average weight for age and height, we would have discovered only 18 of the 184.

If we had X-rayed only the 35 of the entire 1000 who, on rather more careful inquiry than could usually be assumed, were found to be exposed, or to have been exposed, in their homes, to a case of pulmonary tuberculosis, we would have discovered eight of the 184,—one out of 23; and if we had included all with probable, as well as known, history of contact, we would have discovered 17, or one in eleven.

If we had selected for X-ray examination only the 24 in whom suspicious pulmonary signs were detected at the physical examination, we would not have found one.

VIII

SELECTION OF CASES FOR SUPERVISION

In order to translate the results of such a project into practical terms of proper disposal of the cases found, it is necessary to consider in each case the tuberculosis findings, the general health of the child, and its exposure to contact with the disease.

In doing this we have used the classification of childhood type of tuberculosis published by the National Tuberculosis Association as part

of their new *Diagnostic Standards*. This classification is described as follows:[3]

"GROUP 1. OBSERVATION CASES.

"This group should have prophylactic treatment, such as may be obtained in well supervised open-air or window schools, preventoria, or summer camps.

"(a) Cases with small pulmonary or tracheobronchial tuberculous lesions that are becoming calcified. Symptoms absent or ill defined.

"(b) Suspects—children who react to the tuberculin test and who show abnormal X-ray densities at the root of the lung, which may be due to caseous lymph nodes but which are not sufficiently characteristic to justify a definite diagnosis.

"(c) Children who react positively to the tuberculin test, who do not have any X-ray evidence of disease, but who are in poor general health from an undetermined cause.

"(d) Children who react positively to the tuberculin test, have no X-ray evidence of tuberculosis, and are apparently in good health, but who have been subjected to heavy exposure to a source of infection. Also similar cases in which further contact with a pulmonary case cannot be prevented.

"GROUP 2. MANIFEST DISEASE.

"This group should have sanatorium care or its equivalent, whether symptoms or physical signs are present or absent.

"(a) Cases with diffuse or circumscribed infiltrations of the lungs.

"(b) Cases with uncalcified tuberculous tracheobronchial lymph nodes.

"(c) Cases with numerous pulmonary tuberculous lesions or large masses of tuberculous tracheobronchial lymph nodes, even if partially calcified.

"Children in this group have poorly walled off caseous lesions from which dissemination of the bacilli can take place and cause the adult type of pulmonary tuberculosis, miliary tuberculosis, or bone and joint tuberculosis.

"GROUP 3. APPARENTLY HEALED.

"Demonstrable tuberculosis of the lungs or tracheobronchial lymph nodes, or both, which is shown by X-ray examination to be well healed by fibrosis or calcification, or both. No clinical symptoms. These patients usually react to tuberculin. When the tuberculin test is negative, the lesion may be considered obsolete."

The results of applying this scheme of classification to our thousand children are shown in table 16 and diagram 19.

[3] *Tuberculosis of the Lungs and Tracheobronchial Lymph Nodes*, National Tuberculosis Association, ed. 9, January, 1931.

Group 2 (manifest disease) and group 3 (apparently healed lesions) are well defined, with definite criteria for selection and treatment.

Group 1, on the other hand, is a large, loosely organized class, depending a great deal on the arbitrary judgment of the examiner. (Diagram 20.) Yet it is perhaps the most important group. Subdivisions a and b of this group include a little over half of our children with lesions. These are the children for whom the balance has not yet been swung which will determine whether they shall go ahead to the safety of group 3 or slip back into the dangers of group 2.

TABLE 16

Classification for supervision: by tuberculin reaction and by sex

TUBERCULIN REACTION	GROUP 1					GROUP 2				GROUP 3	TOTAL
	1a	1b	1c	1d	Total	2a	2b	2c	Total		
Negative	0	0	0	0	0	0	0	0	0	11	11
?+/1.0 and +/1.0	5	8	14	7	34	0	0	0	0	13	47
++/1.0	0	1	3	0	4	0	0	0	0	0	4
+/0.1	3	1	13	3	20	0	0	1	1	4	25
++/0.1	9	14	15	10	48	0	0	2	2	11	61
+++/0.1	34	22	18	23	97	2	0	10	12	29	138
++++/0.1	0	1	0	1	2	0	0	0	0	3	5
Total	51	47	63	44	205	2	0	13	15	71	291
By sex											
Boys	25	37	26	30	118	2	0	12	14	45	177
Girls	26	10	37	14	87	0	0	1	1	26	114
Total	51	47	63	44	205	2	0	13	15	71	291

When the children have lesions demonstrable by X-ray we have some basis for our decisions as to the significance of their disease. It is much more difficult to form an opinion about those in whom for some reason we cannot demonstrate the lesion. The tuberculous infection indicated by a positive intracutaneous reaction in 673 cases could not be demonstrated in 479 of them. We may assume that these 479 children fell into two classes: one in which the child was apparently taking care of the infection successfully, as evidenced by absence of localizing signs or symptoms and general good health; and another in which the child was apparently not taking care of the infection, as indicated by general symp-

toms of ill health, such as undue fatigability, malaise, failure to gain weight, or slight fever without other cause.

There are two reasons why such an active lesion is not easily demonstrated. It may be outside the pulmonary-tracheobronchial area. X-ray might reveal calcium in the mesenteric lymph nodes, or in the

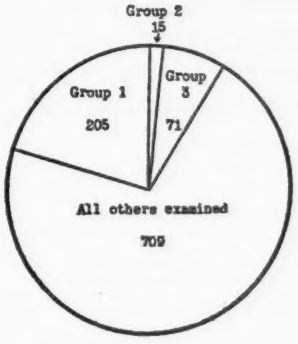

DIAGRAM 19. Classification of the 1000 children according to the scheme recommended by the National Tuberculosis Association.

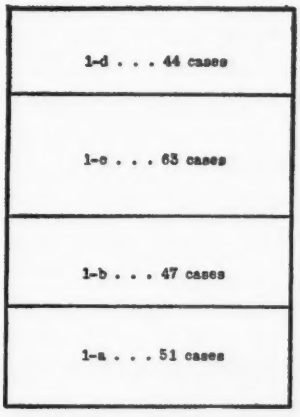

DIAGRAM 20. Composition of group 1 (observation cases).

cervical lymph nodes, but the technique for this is not yet generally employed. Or it may be that the lesion is located in the pulmonary-tracheobronchial area, but is not calcified or fibrosed, and therefore is of the same X-ray density as the surrounding tissues. These cases form a most important group. If, after a child has had all demonstrable defects

corrected, he continues below par without any apparent cause, a single negative X-ray should not be allowed to give a false sense of security. In order to ensure regular supervision, these cases are placed in the observation group, constituting subdivision c of group 1.

The criteria of selection for this group must be arbitrary. We included all children with positive tuberculin reaction who were in poor general health (grade D). When no other explanation for the poor condition, aside from the tuberculous infection, was discoverable, children 10 per cent or more underweight were arbitrarily placed in this class. This gave us the comparatively large number of 63, or about 9 per cent of all the children with positive reactions. We must remember, however, that we found (page 616) a larger proportion 10 per cent or more underweight among those who were negative to tuberculin than among those with a positive reaction. This raises the question whether we are justified in assuming that tuberculous infection is the cause of the underweight in these cases, and whether these children might not more properly be cared for in a pediatrics than in a tuberculosis clinic.

The value of subdivision d of group 1 depends on the accuracy with which the facts concerning exposure to contact can be obtained. This would be more easily done as part of an established tuberculosis service than in a project of this type. In our group there were 44 cases in this class.

Since these two groups (1c and 1d) together constitute over one-third of the cases assumed by this classification to need further supervision from a tuberculosis clinic, they would add greatly to the case-load of such a service, and each individual should be carefully studied before being finally accepted. This cannot be done in one examination.

IX

SUMMARY AND DISCUSSION

It is generally accepted that, among children living in urban communities, tuberculous infection is widespread and occurs at a comparatively early age. The urgent question now is, how best to distinguish, among the infected children, those whose infection has already progressed to active disease, or may do so in the immediate future, in order to ensure for them adequate preventive and curative care.

In a large city the cost of an intensive study of all children would be almost prohibitive, and it is therefore important to find some method of

selecting from the general child population a smaller group which will include all children infected with tuberculosis, so that they may be more intensively studied to determine the significance of their infection.

Almost any factor relevant to tuberculosis might be chosen to act as the general selective agent, serving as a screen to catch and hold in one group those children who need further study. In evaluating the efficiency of any screen, we must consider both tuberculous infection and tuberculous "disease." There will be a large group of infected children from which we must again screen out those in whom the tuberculosis is of clinical importance. Screens will vary as to cost and complexity of procedure, as well as in efficiency, depending on the characteristics of the particular group under consideration.

In this project we have considered the following factors as possible screens:

1: General group characteristics
2: General health conditions
3: Weight
4: History of household contact to tuberculosis
5: Tuberculin test
6: X-ray

1: General Group Characteristics: In communities in which a group known to be especially susceptible predominates, it might be worth while to use this as a screen; but in New York and other large cities there is so little group unity and tuberculous infection is so widespread that no one sex, age, racial, or economic group could be separated out which would include the greater portion of the infection. We have seen (table 10) how evenly the infected and noninfected children are correlated with the various group factors and the customary indices of economic and social status give us no reliable clue as to prevalence of infection.

2: General Health Conditions: From a pediatrics examination much more complete than is practicable in most school medical examinations, we could not predict in any way which children would be shown to have tuberculous infection (by positive reaction to tuberculin) or lesions (by X-ray). This would not therefore be an effective screen to select the group for study, although the general health grade is a prerequisite to the final classification for disposal of cases.

3: Weight: Weight is an enticing screen because it is so cheap and easy to apply. We have found it however to be untrustworthy. One might suppose that if

we selected all children 10 per cent or more underweight, the group would include practically all of those with lesions and most of those with infection. Among our thousand children, however, only 12.2 per cent of those infected fell in this class, and only 9.8 per cent of those with lesions. It is apparent that the utility of this screen would be greatly affected by the racial and economic constitution of the group, and that weight comparisons based on general tables for the average American child are of little value.

4: History of Household Contact with Tuberculosis: While we realize that the incidence of infection is greater among children in contact with tuberculosis, it seems to us that the history of such contact fails in two ways to satisfy the requirements for an effective screen.

First, it would be impossible to obtain sufficiently accurate information without a skilled field investigator. Such an intensive inquiry is a more appropriate function of an organized tuberculosis service than of a project of this kind. The histories in this project are of more than average accuracy and yet only 99 cases of actual or probable contact were obtained. These included only 69 of the 673 infected children and only 17 of the 184 with lesions. If we had depended on this screen we would have missed most of our cases.

Second, in a city like New York, tuberculous infection is so widespread among the general population that household contact is only one of the many sources of infection to which children are exposed, and we should be ignoring the large group in whom the infection occurs outside the home.

5: Tuberculin Test: The tuberculin test is a comparatively easy and inexpensive screen to apply. The technique of intracutaneous injections and reading of reactions can be mastered by any careful, trained worker. Suitable tuberculin is easily obtainable and not too expensive, and the apparatus is simple and inexpensive. The use of this screen is limited in most places by the necessity of obtaining the consent of parents. In our own group by coöperative effort we were able to obtain permission for 70 per cent of the total number of eligible children. The securing of parental consent in respectively 92 per cent and 90 per cent in two schools indicates that with more planning and education a larger number might have been obtained. As a screen, the test does separate the children into two large groups, one including those who have some tuberculous infection needing further study, and the other including those who have no infection, or in whom the infection is so completely healed that allergy is lost. The acutely ill cases in which allergy is also lost need not be considered here. This gives us our first big grouping for further study.

6: X-ray: To X-ray all children would have the advantage that there is rarely any parental objection to it. It is however an expensive screen and gives only

limited information. It would separate out all children with demonstrable pulmonary and tracheobronchial lesions. In the absence of any other test, as of negative tuberculin, it would be more than ever difficult to differentiate the nontuberculous lesions. It would also be difficult to tell, from the X-ray alone, in just which clinical class the case should be placed: whether among the observation cases, in the group with manifest disease, or among the apparently healed. Furthermore, it would give no information about the comparatively large group of children with tuberculous infection who are in need of care even though the lesion is in such a position or of such pathological constitution that it cannot be seen on a film. By the X-ray we would have found the 184 children with lesions, but would have missed the other 500 who were also infected. As we have seen, in our final classification there were an additional 107 among these 500 who needed continued observation. It is quite possible that some of these 107 are even more in need of supervision than those with demonstrable, apparently healed, lesions.

To study thoroughly the incidence of tuberculous infection and disease in a group, it is our conclusion that the procedure must include the following elements:

A test of the entire group by tuberculin,—to screen out those with significant tuberculous infection.
X-ray of the positive reactors,—to discover lesions demonstrable in the pulmonary-tracheobronchial area.
A complete pediatrics examination of the positive reactors,—to evaluate general health conditions as contributing factors.
A final decision as to further care of the positive reactors, made after a careful study of tuberculosis findings, general health condition, and amount of exposure to the disease.

Of course the ultimate aim of all of this study is to help us practically to group our children so that they may receive necessary and appropriate care for their tuberculosis, and at the same time enjoy as much as possible of the normal life and development of a child. From this point of view, it is interesting to review the individual classes; and it is perhaps simpler to start with the group in which sanatorium care may be indicated.

Of the fifteen who had manifest disease, only two had parenchymal infiltration. These two should have sanatorium care. One, a boy of fifteen, had a typical "adult" apical lesion with practically no symptoms, although he was 18 per cent underweight. We have discovered that his father also has tuberculosis, and two other children in the family have been placed under the observation of their district clinic. This family

therefore presents definite conditions which will require nursing and social-service assistance for some time. The other, a boy of 14, had a minimal amount of apical infiltration which resembled a so called "latent apical" lesion. Despite the fact that this boy is 17 per cent underweight, he feels well and is never ill. There is no known source of contact. It is difficult to persuade such a boy to go away to a sanatorium. A satisfactory alternative might be to keep him at home under careful clinic supervision, with additional food and rest, educating his family to consider his condition as a problem with which they must deal over a period of several years.

The other thirteen were placed in group 2c, because of the extent of their lesions, even though most of them were partially healed. All of them are doing well, and with a less extensive lesion would have been put in the observation group (1a). They, too, need supervision, food, rest, and education for their families. These children are not quite able to carry on all the normal activities of their age-group, but it seems hardly necessary to arrange sanatorium care for them. We believe they could be cared for in the city by means of special day schools.

A school similar to Lymanhurst, in Minneapolis, would ensure for these children responsible medical supervision, rest and food, and a school program fitted to the individual's physical and mental capacity. If the child failed to do well a period of bed-rest and observation in a hospital could be arranged, to decide whether transfer to a sanatorium was necessary. If his physical condition continued to improve satisfactorily, he could at the same time continue his school work and eventually be able to join his age-group in the regular grammar school without loss of time or credits. It would be the responsibility of the school and the Department of Health during this time to help the family grasp the real significance of the situation, and to plan wisely for the child's home life,—sufficient sleep in a separate bed, undisturbed by family activities, good health habits; proper food; care of small defects as they arise, before they become gross.

This would seem to be better than to send the child to a sanatorium for a few months. When he returns, it is to a family which has rebelled against his absence, and which welcomes him home with open arms, but with no appreciation of his needs. All too often he soon loses all that he gained at the sanatorium. In addition, more or less of a break has occurred in his school program and it is difficult for him to rejoin his class.

Besides making it possible for many children to remain at home instead of going away to sanatoria, such a day school could render another important service in offering to the child discharged from a sanatorium a sort of half-way station where he could remain for a short time, and where, by means of graded activities, the adjustment could be made less drastic than if he were to enter regular school immediately.

Groups 2c, 1a, and 1b seem to us to need the same type of basic care, varying, as they continue to improve, in the amount of medical supervision required. As a tentative schedule, those with extensive lesions might be examined and X-rayed every three months for a year or so; then every four or six months, depending on the individual indications.

When a child is ready for group 3—apparently healed—he could easily be transferred to a regular school, and his record could be sent to the district clinic, which would then become responsible for his supervision. He might be examined and X-rayed three months after his transfer to the new school, then after six months, and then once a year. We think that it will be safe for our group of 71 apparently healed cases to attend regular school, reporting to their district clinics for examination and X-ray once a year.

Group 1c, children reacting to tuberculin and in poor general health, but without demonstrable lesions, forms a most important group, in which each case requires an individual decision. Is there a lesion outside the pulmonary-tracheobronchial area? Or is it so new or so tiny that our methods for demonstrating it are inadequate? Or can we discover some other cause for the general ill health? These are the questions for which we must try to find answers by continued observation and frequent examinations.

It seems to us that this group should be cared for by a Children's Clinic such as is conducted by the Department of Health at Bellevue-Yorkville. The physician works in close coöperation with the physician in the Children's Tuberculosis Service, both being capable pediatricians with additional training in tuberculosis in children. The same X-ray service is available for both. The same Department of Health nurses handle the cases, under the generalized nursing service, in which one nurse is assigned to a school and its surrounding area. A tuberculosis consultation is always obtainable, and the other pediatrics problems receive more attention than could be given them in the tuberculosis service alone. Poor nutrition is one of the main factors causing a child to be placed in class 1c, and needs special attention. In the Children's Clinic a consul-

tant in nutrition is present at each session, to advise the mothers and children directly about individual problems.

With group 1d, whose members are or have been in close contact with a case of tuberculosis, we must of course make every effort to remove the case from contact with the child or to ensure proper precautions. In addition, the child should be examined and X-rayed once a year at least, and oftener if any suspicious symptoms develop, for it is in this group that we find our highest incidence of lesions developing in adolescence. Since most of these families are already known to the district tuberculosis clinic, it usually seems most advantageous to carry the child contacts as part of the Children's Tuberculosis Service. Children in these two groups (1c and 1d) are the natural candidates for a preventorium.

The behavior problems arising in children with any chronic illness must be wisely dealt with, if the child is to make adjustment to normal life. Tuberculosis is a terrifying word to most parents, and a child with the dread disease becomes the centre of attention in the family circle. Often the other children in the family begin to suffer in health, because the sickly child gets more than his share of the food and care available for the entire family. Caution must be exercised also not to make the tuberculous child feel that he is different from other children or that having tuberculosis carries with it any stigma.

For a family to hold steady and carry on a sane program over a period of years will require sympathetic help and guidance. We shall be setting very high standards for their economic level, and the public-health nurse must have sufficient background, training, and imagination to show them how to make the necessary adjustments. The services of a psychiatrist or a psychiatric social worker have been found to be of great value in helping the nurses to meet such problems.

Tuberculosis in children must be viewed in relation to all the other aspects of the child's life: physical, mental, emotional and economic. In curing the tuberculosis, we must be careful not to ruin the child.

Part 2

SOME GENERAL IMPLICATIONS OF THE STUDY

An investigation of this sort would be much more limited in its value were it not for the well-founded concepts of the pathogenesis of tuberculosis which now dominate our thought. While it is now more than fifty

years since Parrot formulated the law that the lymph nodes of the tracheobronchial region constantly participate in the disease resulting from first infection of the lung, it is only within more recent times that clinical discussion of the problem has been held reasonably well within the channels of orderliness first defined by that law. To Parrot, Küss, Albrecht and Ghon is due fitting acknowledgment for creating and nurturing to full vigor the fundamental ideas which to-day determine our attitude toward tuberculosis as it affects children. To the clinician two of the most important facts are these:

1: In all first infections of the human body with the tubercle bacillus, the regional lymph nodes of the part affected become diseased practically simultaneously. This characteristic linkage of primary lesions has been called by Ranke the primary complex.
2: First infection usually occurs in childhood and the site of the resulting lesion is, in probably 90 per cent or more of the cases, in the lungs and their regional (tracheobronchial) lymph nodes.

The first of these principles is so well founded on pathological and experimental evidence that it is no longer debatable. The second is equally sound though it has been more difficult to prove because of the exacting work required. The evidence is obtained almost exclusively from postmortem study of human organs. In one of their most recent publications, Ghon and Kudlich (1) tabulate the results of such studies in cases of infants and children collected since 1909 in Vienna and Prague by H. Albrecht, Foedisch, and Ghon and his associates, Winternitz and Kudlich. In a total of 2,114 cases examined, evidence that the lung was the primary portal of entry was found in 2,028, or 95.92 per cent. From the work of others there seems to be no reason to doubt that these findings approximate actual conditions in other parts of the world. Cases of infants and children are most suitable for the study of this point because experience has shown that the picture is not often clouded by the lesions resulting from reinfection which characteristically begin to put in their appearance during adolescence.

These simple and sound fundamentals must be accepted as the point of departure in any attempt to discover the presence and meaning of tuberculosis in children. Against such a background it is of interest to try to interpret some of the findings of the investigation reported in the foregoing pages.

Incidence of Demonstrable Lesions: In 489 (72.7 per cent) of 673 adoles-

cent children known to have been infected with the tubercle bacillus (as proved by the tuberculin test), no tuberculous lesion could be demonstrated. In 47 cases (6.9 per cent) the X-ray evidence of a lesion was equivocal. In the remaining 137 cases (20.4 per cent) there were abnormal densities in the X-ray films which we took to represent tuberculous changes. The number of cases with such changes is, therefore, rather large in our series as compared with some others. Some authors estimate that not more than 5 per cent of these "primary" lesions are demonstrable. Our findings, however, approximate closely those of Hetherington, McPhedran, Landis and Opie (2), since a study of their tabulated figures shows that probably at least 20 per cent of the children in this age-group examined by them had demonstrable tuberculous lesions. Variations in the findings of different workers naturally raise the question of accuracy of observation and interpretation. We have come to realize that the mediastinal region, the pulmonary hilum and the parts adjoining it are peculiarly difficult to portray accurately in the X-ray film, that even with reasonably good technique it is impossible to eliminate completely the confusing effects of motion imparted by the heart and blood-vessels, and that the best of technique does not always preclude the possibility of misinterpretation of normal structures which in their X-ray shadows may simulate tuberculous deposits. These peculiar difficulties have been materially elucidated by the work of McPhedran (3), and there is an extensive foreign literature on the subject too lengthy to be cited here but which merits the study of those who are interested in the subject. In our own work we have tried to meet the most exacting conditions that can be applied to-day in the clinic organized for routine work; that is, attention to technical details as described in the first part of this paper, an awareness of common causes of misinterpretation and a dependence on definitely abnormal shadows as the only justifiable basis of diagnosis.

There is really no good reason why, aside from the factor of personal judgment, one should not expect a rather large variation in the percentage of lesions demonstrable in different communities, particularly if we accept the thesis that the incidence and severity of lesions run roughly parallel with mortality rates. Drolet (4) has called attention to the greatly varying tuberculosis death-rates in different sections of New York City, and has shown that in certain areas of the Bellevue-Yorkville district, from which many of our children were recruited, the rate for 1928 was above 350 per 100,000 population, whereas for the city as a whole it was only 89. While no one has ever demonstrated how close is the paral-

lelism between mortality and morbidity in this age-group, it must be assumed on general principles that a similar examination of all New York City children would show a considerably lower incidence of demonstrable lesions than that of our particular group.

Location of the Lesions: In our 184 cases in which definite or probable tuberculous lesions were discovered by X-ray examination, these were visualized in the pulmonary parenchyma alone in 26, in the tracheobronchial region (lymph nodes) alone in 89, and in both these regions together in 69. Realizing that many more tracheobronchial than parenchymal lesions must remain undiscovered by this method, it appears evident that lymph-node disease is the chief problem in this group just as it is in younger school-children. This is further emphasized by the finding that the parenchymal lesions were on the average much smaller and apparently less significant than those of the tracheobronchial lymph nodes. This observation gives support to the assertion of Engel (5): "Clinical consideration of the primary complex is mainly the clinical consideration of bronchial gland tuberculosis. Manifestations of disease predominantly from the side of the primary affect [parenchymal focus] are extraordinarily rare."

Immediate Significance of the Lesions: In chronic pulmonary tuberculosis of adults it is relatively simple to determine the clinical status of the individual case and to determine the need for treatment. In children, however, most clinicians find the decision more difficult to make.

Considering the general behavior of the disease in different age-groups, it is apparent that tuberculosis is not so devastating among children thirteen or fourteen years old as it is among older persons or the very young. Indeed, a careful statistical analysis would probably show that, at least in some communities, tuberculosis is less fatal at or about this time of life than at any other. For illustration we may take several isolated correlations which admittedly are only very approximate and which are selected because they stand in great contrast. These concern the ratio of tuberculosis mortality to tuberculous infection (percentage of the population reacting to tuberculin) in New York City in infancy (up to one year), in the age-period 10 to 14, and in the period 30 to 34. So far as the incidence of infection is concerned it seems reasonable to assume that this is approximately 10 per cent in the first group, 50 per cent in the second and 90 per cent in the third. According to Drolet's tables the tuberculosis death-rates per 100,000 population in 1928 were for these three age-groups (in round numbers) 75, 15 and 90, respectively. On this basis,

therefore, the mortality rate for each 100,000 of the *infected* population would be 750, 30 and 100, respectively. Allowing for considerable error in our estimates, the fact still stands that while a majority of our children are infected with the tubercle bacillus by the time they reach fifteen years, the age-period immediately preceding this time carries with it a peculiarly high measure of protection against fatal tuberculosis.

Further evidence on this point is our failure to find advanced grades of tracheobronchial lymph-node tuberculosis among these 1000 children. By this we mean large, swollen and caseating lymph nodes, filling large sections of the mediastinal space and bulging into the lung field so as to be easily visualized by the X-ray. This may be explained to some extent by the supposition that such severe forms of the disease would give rise to clinical symptoms, keep the child from school, and thereby automatically eliminate him from our study. But this is not invariably so because we know that symptoms may be slight even with well-developed lesions. Furthermore, the careful observations of Engel (*loc. cit.*) indicate that our findings represent the average situation in actual practice. Engel has come to the conclusion that extensive tracheobronchial lymph-node tuberculosis, judged by its distribution in this chain of lymphatic structures as well as by the size of the diseased nodes, occurs as a rule only in early childhood. "In the school-going age one finds but seldom such a process; more often one encounters localized limited foci some of which reveal the signs of retrogression."

Another observation that speaks for the mildness of the disease discovered in these children is the scarcity of extrapulmonary foci. It is generally granted that lesions of serious moment often allow the escape of bacilli into the blood-stream, thus giving rise to a fatal generalization or probably more often to one or more metastatic lesions in some more or less distant part. In only one child was such a lesion found (suspected tuberculosis of the hip joint). We discovered no tuberculides of the skin, no phlyctenular conjunctivitis, nor any other lesions referable to such a cause.

While 15 lesions were classified according to the new scheme of the National Tuberculosis Association as "Manifest Disease" we concluded that only two were so serious as to require immediate sanatorium care. The other 13 cases, while obviously in need of special attention, were not so threatening.

In sum, therefore, we detected in these children a considerable number of tuberculous lesions, the great majority of which, however, seemed

healed or well on the road to healing and not of great seriousness so far as immediate threat to health and life is concerned. For reasons mentioned it appears that this is an average situation as regards this age-group. Why these children should harbor a great deal of tuberculous infection and still be suffering so little on account of it is a matter for study. Krause (6), in his paper, *Human Resistance to Tuberculosis at Various Ages of Life*, concludes that such phenomena are related little, if at all, to the inherent attributes of age itself, and his reasoning is hard to dispute. Our attempt to rationalize the observed facts leads briefly through the following line of thought. In the early years of childhood, particularly in infancy, heavier infection is more often acquired largely because of greater intimacy of contact with tuberculous persons. Heavy infection at this or at any other age-period usually results in extensive lesions. Such disease often spreads rapidly because relative specific immunity has not yet had time to develop, and in most cases it is swiftly fatal. The issue is determined soon after infection is acquired and there is relatively little chronic disease; the victims die soon and the survivors harbor comparatively small lesions. Having survived because their lesions are small, these children then go on to heal their disease, meanwhile developing a specific immunity which *under the conditions of childhood* proves to be a uniquely effective protection against the development of progressive disease. Children who escape infection in their early years are less likely to have intimate contact with tuberculous persons and therefore less likely to be heavily infected. For the same reason, therefore, they are more likely to be added to the "immunes" rather than to the victims.

Why tuberculosis again becomes a more serious and more fatal disease in adolescent and adult life is a question just as intriguing, but it cannot be discussed here. It involves the effects of waning immunity and allergy (11 of our children with healed lesions did not react to 1 mgm. tuberculin and there must have been others with this peculiarity whose lesions we could not demonstrate), as well as the much debated possibilities of endogenous and exogenous reinfection.

The Potential Meaning of the Lesions: While the yield of actual clinical tuberculosis was not great, this search was not by any means barren if we remember one of its chief purposes, namely, to cull out cases of *potential* clinical disease in which by proper prophylactic care this calamity could be averted. The work of Opie and his associates and of Rathbun, Chadwick, Myers, and others demonstrates beyond doubt that these "primary" lesions are the seeds from which spring a certain amount of the

clinical disease of later years. There is, of course, nothing new about this conception, but their methods have brought us nearer to a real grasp of the problem. It can now be said with a considerable degree of assurance that the chance of a childhood lesion developing into outspoken disease later in life depends a great deal on the state of healing and extent of that lesion. The smaller and the better healed it is, the less is the danger. There are other *approximate* methods to estimate this danger, such as a knowledge of the duration of contact with a source of infection and observation of the intensity of tuberculin reaction. In regard to the latter factor, our experience coincides with that of other workers; that is, cases with fresh or very imperfectly healed disease tend to react more intensely to small doses of tuberculin than do those with well-healed disease. Yet, when one applies these measures in an attempt to estimate the hazards in the individual patient, there can be no *immediate* answer. When the lesion is obviously progressive, or gross and fresh, or very poorly healed, or where it is small and obviously well encapsulated and calcified, the decision is relatively simple. But with the larger percentage of cases intermediate between these extremes one cannot rely for a rapid decision on any one feature of the case and usually not even on a combination of features. A period of observation is necessary to study the course of the disease and its symptoms, and this may mean months or years. All such cases are "clinically important" if, as we have suggested, they require some form of frequent or occasional check-up in the school or the clinic. We are fairly familiar with "group trends," but the probable fate of the individual case cannot be so easily anticipated. Here we are confronted with the fact that the issue of human tuberculosis is a very relative thing in the sense that it depends on a host of social, economic and personal factors, as well as anatomical, physiological and immunological ones. Whatever may be the developments of the future it is hard to see how we shall ever be able to formulate accurate judgments without a methodical study of all these features in every case.

Limitations of This Method of Investigation: A search of this kind, for these reasons, leaves some gaps. In our particular study the general pediatrics examination alone was valuable because of the many defects it revealed in these children, but, in estimating its use in relation to tuberculosis findings, we realize further work is necessary. Generally speaking, the method sufficed to "screen out" cases with obvious or suspected lesions and then to classify these for disposition. Most of the cases (205) go into the observation group, which means that no community should

consider its machinery adequate unless it provdes for such necessary observation. What this machinery should be and just how much tuberculosis will actually be prevented by its employment must necessarily vary according to local conditions, but both of these questions need further investigation.

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Correction

Through an unfortunate error the three legends of figs. 1, 2 and 3, accompanying the article by Doan and Moore, April REVIEW, 1931, vol. xxiii, pp. 409–421, were separated and placed under the charts on pages 413, 414 and 416. The legends all belong to plate 1 on page 418, and describe the three figures of this plate.

PULMONARY ASBESTOSIS II

Including the Report of a Pure Case[1]

KENNETH M. LYNCH AND WILLIAM ATMAR SMITH

For a number of years one of us (W. A. S.) has observed, in the chest clinic at the Roper Hospital (Charleston) and at clinics held in certain sections of Charleston County, cases of respiratory disease which possessed characteristics not ordinarily encountered. The symptoms presented by these patients were cough of varying severity, usually slight but occasionally severe dyspnoea, expectoration and, in some, loss of weight. There were few or no constitutional symptoms. The physical signs consisted in most instances of poor expansion and fine râles at both lung bases. When roentgenograms were obtained they have been interpreted as being "negative" in some cases, as showing moderate degrees of granular mottling in others, and in a few rather extensive fibrosis. Sputum examinations failed to show tubercle bacilli. The occupational history revealed that at one time or another, for periods varying from months to years, these people had worked in an asbestos factory. Several such patients were diagnosed and treated as having pulmonary tuberculosis.

The significance of the relationship of the occupation and the pulmonary disability was realized when in the fall of 1927 an adult male, about 40 years of age, who had worked for 17 years in an asbestos plant, was seen in consultation with a local physician. This man exhibited the characteristic picture of the terminal stage of respiratory failure. He was emaciated, cyanotic and dyspnoeic. He had a severe cough, productive of a large amount of mucopurulent sputum in which no tubercle bacilli were found. The fingers were moderately clubbed, and the nails curved and cyanotic. There was a moderate daily rise of temperature. The expansion was diminished, resonance impaired over the lower lobes, and there were numerous coarse and moderately coarse râles over the entire chest. The roentgenogram showed fairly distinct granular and linear

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opacities at the lower portion of both lung fields, the apices were emphysematous, and there was well-defined "shagginess" about the heart. This man was seen on only a few occasions before he died. No necropsy was obtained. The diagnosis of pneumonoconiosis, possibly due to the inhalation of asbestos dust, seemed justified, and the case was reported as such to the Medical Society of South Carolina.

These experiences led to the conviction that prolonged exposure to asbestos dust presented a very definite health hazard, but until recently the matter had not been subject to proof. That the same impression had prevailed among physicians practising in or near asbestos factories is indicated by the statement of Cooke (1) that "Medical men in areas where asbestos is manufactured have long suspected the dust to be the cause of chronic bronchitis and fibrosis"; and of Sir Thomas Oliver (2), who points out that he has visited asbestos factories in America and has seen cases of pulmonary asbestosis at Armley, Leeds. (He does not specifically state that he has seen cases of this disease in this country.) Simson (3) in the introduction to his article on *Pulmonary Asbestosis in South Africa* says, "It has been known for some time that workers exposed to the dusty atmosphere arising from some processes involved in the preparation of asbestos materials suffer from pulmonary disability." From these expressions it would seem that the baneful effects of asbestos dust were long recognized, but until Cooke's (1) report in 1924, in which he describes the unusual morbid anatomy of the lungs, there was no conclusive evidence of relationship of this dust to pulmonary pathological changes.

As American medicine contains only meagre reference to this subject, it would seem timely to review briefly the progress that has been made in the study of this disease, analyze the cases reported, and at the same time put on record a complete case of pure pulmonary asbestosis, the first, so far as we have been able to ascertain, that has come to necropsy in this country.

The first readily available record of this condition is the case reported by Cooke (1) in 1924, —that of a woman aged 33 years, who commenced work in an asbestos factory at 13 years of age and was almost continuously employed until two years before her death in 1924. Her symptoms were cough, dyspnoea, expectoration and lassitude, all of which gradually increased in severity, being followed later by sweats and fever. Signs were first those of "fibrosis of the lungs" and two years prior to death the signs of cavitation appeared. The

necropsy revealed the peculiar type of pulmonary fibrosis in which granular dark brown pigment was found. There was also fibrocaseous tuberculosis.

In 1926 Pancoast and Pendergrass (4), together with Miller and Landis, examined 17 asbestos workers in the United States, two of whom showed "first stage changes and the other fifteen definite second stage appearance." This was apparently only a roentgen study and the classification was based from the point of view of silicosis. They rather discounted Cooke's findings, believing his fibrosis as likely due to tuberculosis alone.

In 1927 Cooke (5) published a more detailed discussion and elaborated on the subject of asbestosis. He cited the patient observed by Dr. H. Montague Murray at Charing Cross Hospital and reported in the Charing Cross Gazette in 1900. This was a man of 33 years of age who was admitted to the Hospital in 1899 and died in 1900. It is stated that the man informed Dr. Murray that he was the sole survivor of ten men who started work with him in the carding room of an asbestos plant ten years previously. The necropsy showed fibrosis with what Dr. Murray thought were "spicules of asbestos" in the lung sections.

Stuart McDonald (6), to whom was referred a specimen of Cooke's first case for histological study and to whom we are indebted for an excellent description of microscopic appearances of the lung tissue in this disease, refers to a case of Dr. Grieve's, sections from the lungs of which presented "appearances practically identical," death, however, resulting from bronchopneumonia.

Sir Thomas Oliver (2) reports in the same journal that he examined with Dr. Grieve of Armley, Leeds, two women suffering with pulmonary asbestosis. One was 48 years of age and had worked in an asbestos factory for thirty years. She gave up work the year before on account of shortness of breath and cough. She was much emaciated, and expansion of the chest was one inch. The physical signs present were flattening of percussion note at the bases. The breath-sounds were exaggerated at the top of both lungs and diminished at the bases. "Small dry friction sounds" were heard at the right base. "Moist tinkling sounds suggestive of cavity" were heard on the left, and the apex of the heart was displaced upward and outward.

The other patient was 39 years of age and had worked in an asbestos factory 18 years. She developed cough and asthma four years previously. She remained away from work for three months and then worked for three years. She had dragging pains in the chest, shortness of breath, and cough. The chief signs were moist râles in both axillae and small friction with crepitation heard at both bases. No tubercle bacilli were found in the sputum of either.

In 1928 Simson (3) reported four cases coming to autopsy in whose lung substance were found the "golden yellow bodies" now believed to be pathognomonic of asbestosis. The first subject was an adult native South African who had worked in asbestos for one year, and nine weeks before death he developed acute miliary tuberculosis. The second was also a male native who

had worked two years in a mill. He had well-marked lung fibrosis in which the "asbestosis bodies" were readily found. This case apparently died of uncomplicated pulmonary asbestosis. In two other asbestos workers dying of lobar pneumonia Simson also found these characteristic bodies.

In a communication to the editor of the *British Medical Journal*, September 5, 1928, M. J. Stewart (7), in describing his method of "immediate diagnosis of pulmonary asbestosis at autopsy" by squeezing the juice from a small piece of fibrotic lung on a slide to find the "brown bodies" of this disease, reports four cases. One was a woman 34 years of age who had been employed in asbestos work for 16 years. Both lungs were extensively fibrosed, and very anthracotic, but there was no evidence of tubercle, syphilis or silicosis. In the other three cases Stewart gives no details but states that the "asbestosis bodies" were found by Dr. F. L. Taylor in the lungs of these workers after death.

Stewart and Haddow (8), in directing attention to their method of exploratory lung puncture to obtain secretion for examination for "asbestosis bodies," report a case successfully diagnosed by this procedure. They also report the finding of these bodies in the sputum of this and one other patient. It appears that they were the first to suggest the value of sputum examination in the diagnosis of this condition.

Seiler (9), of Glasgow, reported in 1928 a case of pneumonoconiosis due to inhalation of asbestos dust. This was a man of 40 who had been associated with the asbestos industry for 22 years. He had cough, breathlessness, loss of weight, and lassitude for a period of several months. His physical signs and roentgenograms were characteristic of fibrosis of the lung. The patient was still living.

W. Burton Wood (10), of London, in an article on pulmonary asbestosis, which he illustrates with roentgenograms, bases the diagnosis of the 15 cases reported on the occupational history and the clinical and roentgenological manifestations. No record of the finding of asbestosis bodies appears.

In a subsequent article Wood in collaboration with Page (11) reports in detail the clinical and pathological findings on one of these patients who had died. This was a woman, aged 34, of nine years' service in an asbestos factory. She suffered with dyspnoea, loss of weight, and palpitation. She was emaciated and pale, her skin having a violet tinge. The physical signs showed flattening of the left side of the chest, impaired resonance over both bases, and "crackling crepitations of fibroid type" were heard over the whole of the left and the base of the right lung. The roentgenogram showed granular mottling throughout both lungs. The heart was slightly displaced to the left and its left border was obscured by heavy shadows in the lower lung field. At necropsy was found the typical fibrosis with amorphous dark brown pigment and numerous "golden yellow bodies." These bodies were also found in the expressed lung juice. Bronchopneumonia was apparently the terminal event. Later (12) these authors report a similar case, necropsy showing an associated tuberculosis.

Wood and Gloyne (13) recently reported having seen 37 cases, 15 of which were previously reported. In four the diagnosis was doubtful. There were four upon whom postmortem examinations were made, two of which were reported by Wood and Page, the other two being previously unreported cases.

Merewether (14) has recently reported upon a comprehensive group study of asbestos workers for the detection of pulmonary disability. Of 775 workers engaged in the more dusty processes of manufacture 374 were examined. Ninety-five, or 25.4 per cent, of these showed pulmonary fibrosis attributable to asbestos dust, and 21, or 5.8 per cent, were classified as showing a prefibrotic condition. The tabulation of those examined, by years employed in the industry, showed a marked increase in percentage of occurrence of fibrosis, varying from nothing in the first four years to more than 80 per cent affected in 20 years or more of exposure. The diagnosis of these cases was based on the occupational history, and the clinical and roentgen findings. The sputum was apparently not examined for asbestosis bodies.

Lynch and Smith (15) recently reported two necropsies on asbestos workers, one dying of gunshot wounds and one of lobar pneumonia, in both of which the lungs presented deposits of yellowish-brown pigment and asbestosis bodies. Included in this article was a report of four other cases, two of which had associated pulmonary tuberculosis, one syphilis, and the fourth pulmonary fibrosis with progressive cardiac failure.

The finding of asbestosis bodies in the sputum confirmed the diagnosis in three of these. In the fourth it was anticipated that because of the length of exposure and advanced pulmonary disease the exhibition of these bodies would be a simple procedure, while, as a matter of fact, with copious sputum and numerous examinations, none was found. Lung puncture was not attempted.

A Complete Case of Pure Pulmonary Asbestosis

This patient was a white male, 46 years of age when first coming under observation at the chest clinic at Roper Hospital in November, 1925. His physician had diagnosed pulmonary tuberculosis. This opinion was confirmed and he was sent to Pinehaven Sanatorium for treatment. No tuberculosis was known in his family and his history of past illnesses is unimportant.

Occupational History: He commenced work in a local asbestos plant in 1911 or 1912 as a carder, working steadily until 1919, losing two weeks during that year, and four weeks in 1920. He was out in 1921 and worked only three and one-half months in 1922. He was out again in 1923, but worked from June, 1924, to May, 1925, making a total of approximately $11\frac{1}{2}$ years.

Present Illness: In 1914 or 1915 he began to cough and to bring up a

small amount of sputum. In 1918 or 1919 he developed a pain in the lower right chest, which was aggravated by movement, but not affected by the cough or by deep breathing. Shortly after the pain commenced he began to lose weight in spite of having a good appetite. At about the same time he noticed that his breath was getting short. The pain and expectoration persisted, he tired more easily, and breathlessness became more pronounced. In August his left lower chest began to pain him, and in October he expectorated a small amount of blood. He had no fever or night-sweats and did not feel weak. The chest pains, loss of weight (23 pounds), and shortness of breath caused him to seek medical advice.

Physical Examination: November, 1925: A very lean man, 65 inches in height, weighing 97½ pounds, color somewhat dusky, lips slightly cyanotic. The finger-nails were slightly cyanotic and curved to some extent, but not clubbed. The neck veins were prominent. The chest-wall was much emaciated, badly shaped, and of the "cobbler type." Expansion was very poor and unequal, being less on the left. Resonance was impaired anteriorly and posteriorly throughout the left side, and there was bronchial breathing to the second rib and fourth dorsal spine, with moderately coarse and coarse râles practically over the entire lung. On the right side there were moderately coarse and coarse râles to the fourth rib and eighth dorsal spine.

The roentgen report by Dr. A. R. Taft is as follows:

> Examination of the chest with the fluoroscope and film shows considerable amount of mottling in both lungs. Some in right upper but a great deal in left upper, sufficient to completely block the first interspace. In the second left interspace there is some breaking down with cavity formation about 2 cm. in diameter. (See figure 1.)

The examinations of other systems were negative. Sputum tests were negative for tubercle bacilli.

This patient remained in the Sanatorium from November 9, 1925, to January 15, 1926, when he became tired of the restrictions and deserted. During this period his temperature stayed within normal limits, except for one week in December when there was a daily rise to 100°. On the rest regimen he seemed to improve, his cough and dyspnoea lessened, and he gained 20 pounds.

He returned to work in the asbestos plant for several months in 1926, later obtaining employment in one of the city parks as a gardener. In

June, 1927, he was treated at Roper Hospital for acute prostatitis. He returned to the chest clinic at Roper Hospital in August, 1929, on the suggestion of the tuberculosis nurse. Although his cough, expectoration and chest pains were still present he had little complaint except for dyspnoea; the latter had grown progressively worse and was much aggra-

FIG. 1. CASE 10392. ROENTGENOGRAM, NOVEMBER, 1925

vated by exertion. He had considerable difficulty in doing any work at all. Except for appearing somewhat more "dusky," the physical examination showed little change except that the râles were more widely distributed. A roentgenogram made at this time was interpreted by Dr. R. B. Taft as follows:

There is scattered density throughout the chest. Hilar markings are very dense, and there are diaphragmatic adhesions on both sides. There is probably cavity formation in the middle left, although this is not positive, due to the peculiar appearance of the whole chest. (See figure 2.)

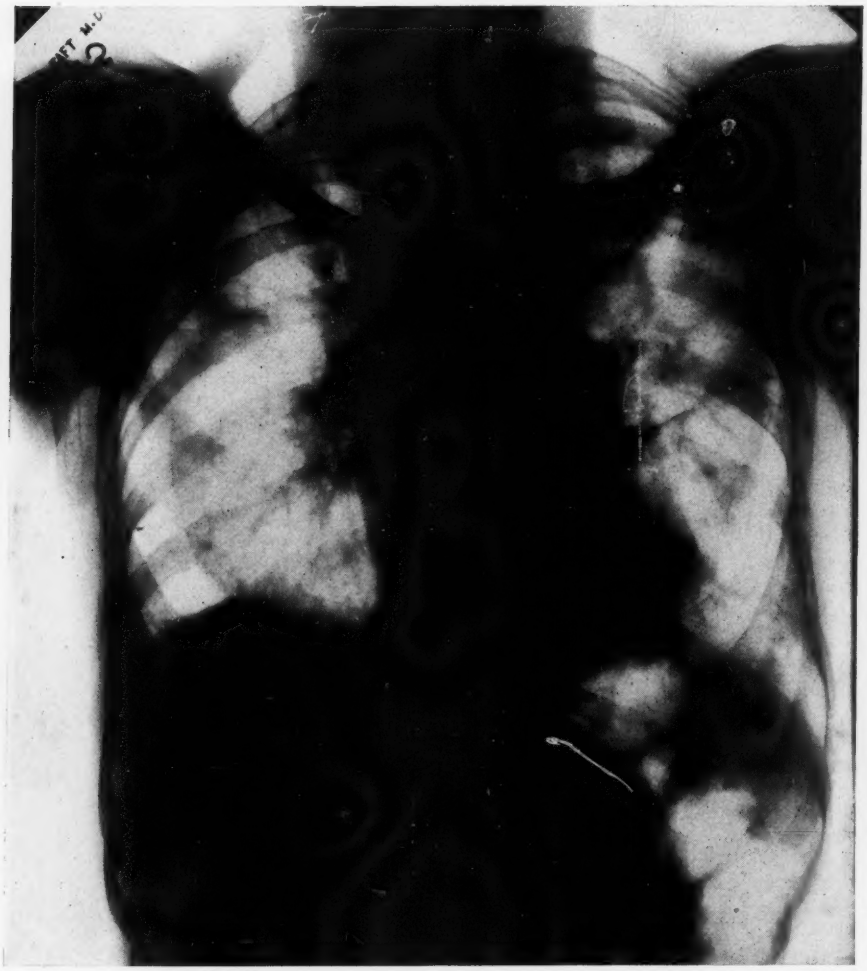

FIG. 2. CASE 10392. ROENTGENOGRAM, AUGUST 27, 1929

He was not seen again until April 5, 1930, when he returned to the clinic seeking hospitalization. His dyspnoea, cough and expectoration had increased, and for the past two months his feet and legs had become swollen. He was weak, emaciated, cyanotic, and the lower extremities

were oedematous. Resonance was impaired over both lungs and there were numerous râles of all sizes over the entire chest. He was admitted to Roper Hospital, where he died of congestive heart failure about three weeks later.

His sputum was negative for tubercle bacilli and for asbestosis bodies on four examinations. The blood Wassermann was negative. The

FIG. 3. CASE 10392. ROENTGENOGRAM, APRIL 10, 1930

haemoglobin was 85 per cent, white cells 7,975, lymphocytes 17 per cent, transitionals 1.5 per cent, polynuclears 75.5 per cent, eosinophiles 3.5 per cent, basophiles 2.5 per cent. The urine showed a trace of albumen and coarsely granular casts on two examinations.

Dr. R. B. Taft's roentgen report of April 10, 1930, is as follows:

There is a large amount of fibrosis scattered throughout both sides with evidence of a cavity in the middle portion of the left, and a larger cavity in the middle portion of the right. Both of the apices appear to be evenly consolidated which suggests a small amount of fluid causing a partial collapse of the lungs. Heart and mediastinum are very much displaced to the left." (See figure 3.)

Autopsy

No. 10392: The body had been embalmed prior to the autopsy. There was marked subcutaneous oedema, especially of the feet and legs to above the knees, and some of the hands and forearms. The toes and fingers were stubby, but there was no cyanosis, perhaps interfered with by the embalming. The sternum was flattened above and definitely depressed over the epigastrium.

The pericardium and heart were definitely displaced to the left, the apex well outside the nipple line at about the fifth interspace. The heart weighed 343 gm. empty, was definitely broadened but not lengthened, the right heart furnishing the breadth, the left not enlarged. The right cavities were well enlarged and open, the left ventricle closed. The right myocardium measured 8 to 10 mm. in thickness well up from the apex toward the pulmonary orifice. Microscopically the muscle fibres were not of uniform size, and there was generally a distinct enlargement of those of the right. They were of indistinct outlines and striations, and those of the right ventricle were frequently vacuolated. There was an increase of stroma, and the veins, particularly of the right, were definitely distended with blood.

The aorta was the seat of a minor atheroma, and the whole vascular system, outside the heart, was in good condition.

Both pleural sacs were completely obliterated by old adhesions, usually very dense, especially over the whole right lung and the upper and lower left. The diaphragm was up to about the fourth rib on the left but was low on the right. The left lung was retracted well over to the outer wall and high, occupying about one-half to two-thirds of the usual space. The pleura generally was thick and cartilage-like, especially over the apex and base. The lung was coarse, leathery, nodular and lumpy over the upper half and the base, the middle being more spongy and air-bearing. The vessels and bronchi were very prominent and the framework coarse; variously there were prominent emphysematous bullae in the parenchyma especially in the apex where there was a group or chain of honey-

FIG. 4. LATE STAGE, WITH EXTREME FIBROSIS OF LUNGS AND HYPERTROPHY OF RIGHT HEART. CASE 10392

combed sacs. The interlobar pleura was obliterated. The bronchi appeared congested. The hilum lymph nodes were inconspicuous, did not appear enlarged, and were smoky black. There was no evidence of tuberculosis.

The right lung was large, filling the whole right chest and encroaching some toward the left. (See figure 4.) Its whole pleura was very thick and cartilage-like. The interlobar pleura was sealed outwardly, but was open, a clean membrane presenting, between the adjacent lobes. The lung was very much like its fellow generally, the upper lobe densely fibrous and lumpy, vessels and bronchi prominent, and a mass of em-

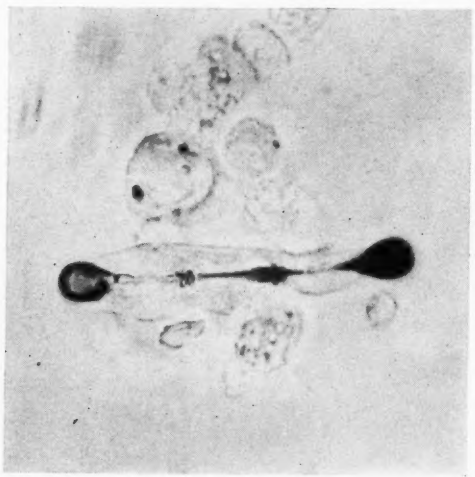

FIG. 5. GIANT CELL PHAGOCYTE CONTAINING AN ASBESTOSIS BODY. MONONUCLEAR PHAGOCYTES WITH GRANULAR PIGMENT. FRESH UNSTAINED SCRAPINGS FROM LUNG SUBSTANCE. CASE 10392. PHOTOMICROGRAPH ×860

physematous bullae in the apex. The middle lobe was not so fibrous, nodular or lumpy, and had prominent bronchi and air bullae. Both lungs, especially the right, bore much frothy fluid, which, expressed and examined, revealed numerous asbestosis bodies, free, in sheaves or clumps, and ingested by giant cells. (See figure 5.) The two ends were often engulfed by different giant cells. There were also a few dust cells, with fine black granular pigment, and masses of a yellowish amorphous substance, of the color of the asbestosis bodies, in cellular debris.

Microscopically there was an extreme grade of hyalinizing fibrosis of the lungs, universally but irregularly distributed. The pleura was thick

and fibrous, and there was marked interlobular fibrosis. Scattered here and there were irregularly rounded areas of hyaline fibrous tissue, in somewhat laminated form, within which were masses of greenish-black granular substance. (See figure 6.) Here were also areas of liquefaction and calcification in the centre of these hyaline nodules. A large part of the alveoli were obliterated or virtually so. Some lobules remained open, the sacs having thick fibrous walls. In these open alveoli the epithelium was sometimes cuboidal and there were fairly numerous

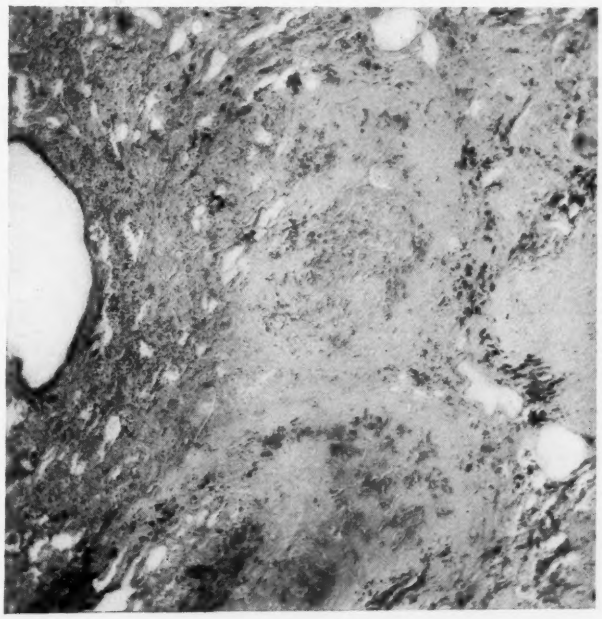

FIG. 6. LATE STAGE WITH EXTREME FIBROSIS AND BRONCHIECTASIS. CASE 10392. PHOTOMICROGRAPH ×57.5

large round phagocytes, some with a group of nuclei, some mononuclear. These macrophages contained black or greenish-black or brownish granular pigment and an occasional asbestosis body. Where the lung was less fibrous there were young connective-tissue cells and lymphocytic accumulations. The bronchioles were dilated and their walls thick and fibrous. In some areas the lobules of alveoli showed marked emphysema, large empty sacs with thin walls. Asbestosis bodies in typical forms, with a variety of architectural figures, yellowish-brown, clubbed, dumbbell and rod forms, were to be found widespread, singly or in groups

within giant cells in the alveoli of less fibrous areas, singly in the alveolar walls and interlobular tissues showing the younger fibrosis. (See figure 7.) Associated with them was much granular substance of the same color, as if from disintegrated asbestosis bodies. Beside these pigments there was much ordinary black anthracotic material around the vessels of the interlobular tissues. The interlobar pleura was especially thick.

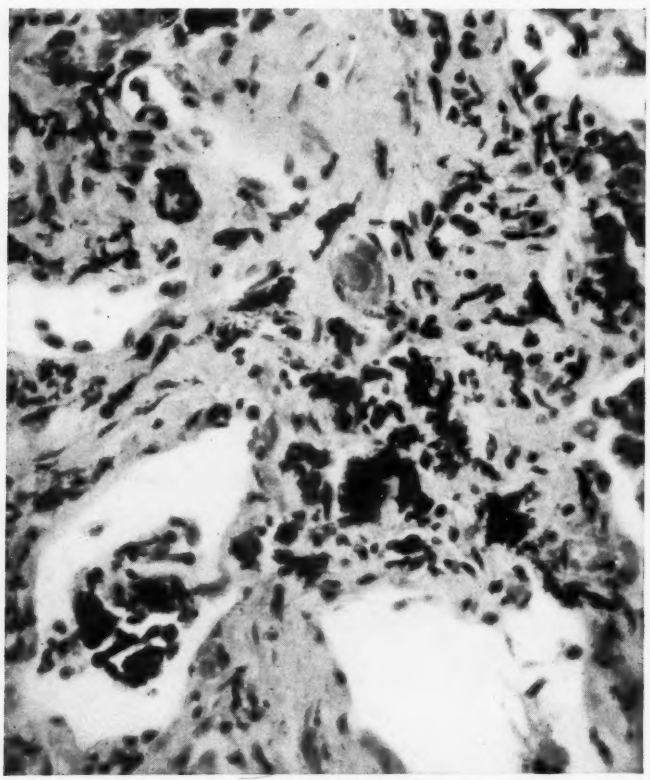

FIG. 7. PROGRESSIVE FIBROSIS WITH ASBESTOSIS BODIES AND GRANULAR PIGMENT IN ALVEOLI AND FIBROUS TISSUE. CASE 10392. PHOTOMICROGRAPH ×280

The large bronchi were practically normal. The peribronchial lymph nodes were the seat of marked fibrosis, oedema, atrophy of follicles, and accumulation of masses of black and yellowish-brown granular pigment, of the same order as that in the lung.

The liver was grossly and microscopically in a state of extreme chronic passive congestion, which state, in lesser degree, was conspicuous in spleen, kidneys and other viscera.

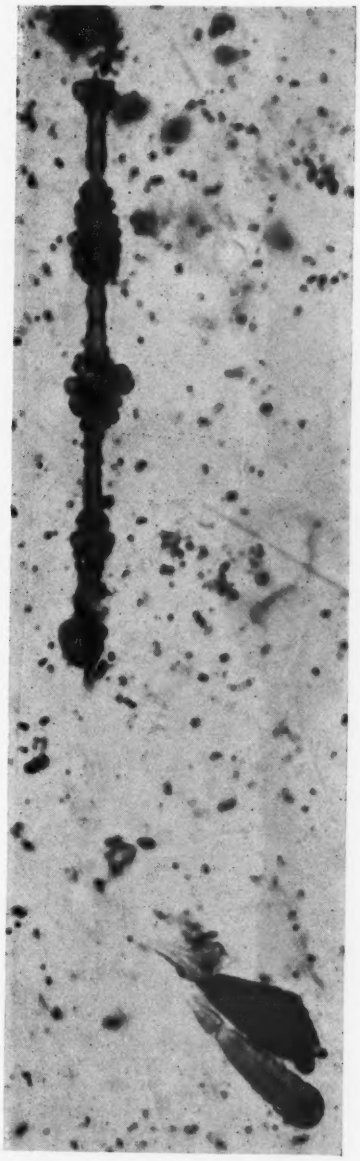

FIG. 8. ASBESTOSIS BODIES AS SEEN IN SPUTUM AFTER DIGESTING WITH 10 PER CENT SODIUM HYDRATE. FROM ANOTHER CASE. PHOTOMICROGRAPH ×950

COMMENTS ON THE CASE

This man entered the employ of a local asbestos plant shortly after it had commenced operation. The factory buildings were renovated old structures which had been erected for other purposes. It has been ascertained that ventilation was extremely poor and no provision had been made for removal of dust at this time. No one suspected the dangerous properties of the dust. It seems reasonable to assume that the man was exposed for many years to air heavily laden with finely powdered asbestos. When this man first came under observation five years before his death his lungs were already irreparably damaged and it was not anticipated that he would survive many months. It was during the last years of his life that the diagnosis of fibroid tuberculosis, which had been made in spite of the absence of toxic symptoms and absence of tubercle bacilli, was questioned. This previous diagnosis was largely due to upper-lobe involvement and to a misinterpretation of the roentgen films.

The irregular dense opacities surrounding areas of translucency, due to emphysema, suggested cavitation, even when reread in the face of knowledge to the contrary. No cavities were found postmortem. There was a small pneumothorax on the right side on a level with the superior fissure, which extended downward, separating the upper and middle lobes. This shows up very well in roentgenograms of August, 1929. (See figure 2.) The other cavities suspected in the roentgenograms were undoubtedly groups of very large emphysematous bullae.

It is remarkable that no asbestosis bodies were encountered in the sputum, as this was mucopurulent and copious in the terminal stages of the patient's illness. These bodies were found in abundance in the expressed lung juice and in the alveoli in lung sections. On account of the extreme fibrosis and the fixed condition of the lungs it is likely that there was very little expulsion of material from alveoli into the bronchial tract. Perhaps in such late cases sputum examination for asbestosis bodies may not be as valuable as in earlier stages.

This is undoubtedly a pure case of long-standing asbestosis, with consequent extreme hyaline fibrosis of the lungs, and consequent obliteration of a large part of air-bearing tissue, emphysema, bronchiectasis, increased pulmonary resistance to the circulation, hypertrophy of the right heart with eventual degeneration, fibrosis and congestion of the heart, progressive heart failure, with generalized passive congestion of the viscera,

and death from slow cardiac failure, the natural end-result of uncomplicated disease of the lungs of this extent and character. It is interesting to note in the lung changes the common laminated hyaline fibrous nodule, which has been described heretofore as a characteristic lesion of the fibrosis of pulmonary silicosis.

SUMMARY

In a survey of all available literature on the subject up to the present time we have collected 172 cases of pulmonary asbestosis. There are references to this subject in one or two abstracts, notably those of Bridge (16) and of Sir Thomas Oliver (17), but specific cases are not enumerated. In four cases belonging to Wood's series the diagnosis was doubtful, and in the majority of others the diagnosis was based entirely on clinical and roentgen findings. There were 27 in which the diagnosis was confirmed by the finding of the asbestosis bodies in the sputum, in the lung juice by puncture, or by necropsy. Necropsy has been made on 18 cases. In three of these the disease was complicated by pulmonary tuberculosis, three by lobar pneumonia, three by bronchopneumonia, and one was a traumatic death. In 4 the authors failed to give a complete report, stating only that the necropsy confirmed the diagnosis. Including the very first case recorded, that of Murray in the Charing Cross Gazette of 1900, which apparently received little attention until resurrected by Cooke, there are now 4 records of necropsy on uncomplicated pulmonary asbestosis. Except those reported by ourselves, and those by Pancoast and Pendergrass, and four others by Simson from South Africa, these cases have all developed in the British Isles.

Since this article was submitted for publication the following report has been encountered: Mills, R. G., Pulmonary Asbestosis: Report of a Case, *Minnesota Medicine*, 1930, xiii, 495. This was apparently a pure case in which death occurred some seventeen years after exposure to asbestos dust in South America.

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ALTERNATING ARTIFICIAL PNEUMOTHORAX[1,2]

I. D. BRONFIN

The principles governing pneumothorax therapy, as laid down by Forlanini, have undergone striking modifications during the past decade. The indications for this form of treatment were at first confined to strictly unilateral cases. Experience has since shown that proliferative and even fibrocaseous processes in the so called better lung, when not too extensive, improve after a satisfactory collapse of the more involved lung has been obtained. The further observation that a moderate reduction in pulmonic mobility instead of complete collapse does not lead to bad results, as was at first believed, but, on the contrary, brings about definite improvement, leads some physicans, in their desire to do something for their apparently hopeless patients who may have developed active disease in the contralateral lung, to the rather heroic measure of simultaneous bilateral compression.

A review of the literature on simultaneous bilateral pneumothorax discloses that the encouraging results reported are not entirely conclusive, for the reason that most of the patients had not been observed for a sufficiently long time. The work of Kinsella and Mattill (1) convinces one that bilateral pneumothorax is feasible in certain cases and for definite emergencies, but the fact that of the 28 patients reported 7 were still confined strictly to bed, 3 were allowed bathroom privileges only, 7 had the pneumothorax discontinued on one or both sides, 1 had to be subjected to thoracoplasty, 9 were dead and only 1 was able to return to work, leaves one in doubt as to the efficacy of this treatment. Kerzmann (2) reports 19 cases, of which several showed marked clinical improvement, but issues a warning that the procedure is justified only when all other measures have failed. The several other reports on single cases or small series do not differ essentially from those referred to

[1] From the National Jewish Hospital, Denver, Colorado, and the University of Colorado School of Medicine.

[2] Read at the annual meeting of the American Sanatorium Association, Memphis, Tennessee, May 6, 1930.

above. It would, therefore, be premature to predict the future evolution of bilateral pneumothorax, but it is safe to assert that its applicability will probably always be limited.

On the other hand, the need for resorting to alternating or successive pneumothorax will continue to increase, since artificial pneumothorax is now more widely employed, and the majority of patients subjected to this treatment in recent years, according to most observers, notably the Matsons and Bisaillon (3) and Matz (4), have bilateral lesions. Reactivation of the old lesion or progression of the disease in the untreated lung is not an uncommon complication. It must also be emphasized that a large number of patients with apparently unilateral disease develop contralateral lesions during pneumothorax therapy. In Rist's (5) series of 759 cases, 278, or 36.6 per cent, had this complication, and of these 179 died, constituting 75 per cent of his total deaths. It seems to us that such complication can be combated more advantageously by discontinuing the first pneumothorax, especially if the latter had had a duration of at least one year or longer, than to subject the patient to the risk of simultaneous bilateral compression.

Alternating pneumothorax was first practised by Forlanini (6). In 1911 he published a report on 2 patients cured of unilateral pulmonary tuberculosis by artificial pneumothorax in whom later he instituted pneumothorax for the opposite lung in order to control a lesion that had developed there. He emphasized the satisfactory respiratory function of the previously collapsed lung after the second pneumothorax was instituted, and stated that this fact disproves the theory of the sclerogenic effect of artificial pneumothorax upon the lung.

In 1926 Rist and Chabaud (7) reported 20 cases of alternating pneumothorax. Of the total number, 7 resulted fatally; in 2 cases exacerbations of the patients' condition were prompt and death ensued soon; 5 remained unchanged and 6 made favorable progress. These figures, the authors point out, can be better appreciated when they are compared with the mortality figures of patients who developed such complications but were not given a second pneumothorax. Three months after the onset of disease in the contralateral lung, 40 per cent of the patients with simple pneumothorax had died as against 16 per cent of those with alternating pneumothorax. At the end of 6 months, the mortality was 60 and 25 per cent, respectively, and at the end of one year the figures were 74 and 40 per cent in favor of alternating pneumothorax. The results from alternating pneumothorax are thus appreciably better, and can be further

improved by early recognition of the lesion and timely institution of this treatment.

Our personal experience is limited to a group of only 16 cases. Only 6 of these patients, however, had been observed for a sufficiently long time to justify a clinical report with a critical evaluation of the results.

Case Reports

Case 1: M. S., male, age 21, occupation salesman, admitted February 24, 1925, with history of prolonged exposure to his tuberculous mother. Onset of pulmonary symptoms in December, 1924, with rather brisk haemoptysis. Cough, chills, fever and night-sweats followed. Physical examination disclosed active involvement of entire left lung and apparently normal right lung. Roentgen-ray film showed extensive exudative process scattered throughout left side, and early peribronchial infiltration of right upper lobe. After strict confinement to bed for one month with no tendency to improvement, patient was offered pneumothorax. Marked amelioration of all symptoms followed third refill, and four months later patient felt so well that he left the hospital, against advice, to return to work. Refills were continued, and patient was able to pursue his occupation until November, 1926, when he noticed gradual recurrence of symptoms, principally cough, blood-tinged sputum and fever. Upon advice of his physician at New Orleans, he returned to Denver and was readmitted in December, 1926.

At this time physical and roentgen-ray examinations disclosed complete pneumothorax on the left side and exudative lesion of right upper lobe. By middle of February, 1927, the partially reëxpanded left lung showed surprising clearing, and, although the same film showed slight decrease in intensity of new lesion on right side, patient continued to pursue active febrile course despite complete bed-rest. The temptation to compress the right lung without further delay was great, but further deliberation favored policy of temporary conservatism on ground that left lung had not sufficiently reëxpanded to determine accurately its physiological integrity, and, second, the patient was apparently not worse. Film taken June 28, 1927, showed that left lung, completely reëxpanded, was only moderately sclerosed but otherwise clear. Right side remained stationary. Pneumothorax was, therefore, now considered a safe procedure. A so called selective collapse was obtained. Improvement with almost dramatic rapidity again set in, and, after eleven months of compression, during which patient was completely free from either local or constitutional symptoms, he returned to work. Refills were administered until August, 1929, when discontinuance became necessary on account of rapidly forming adhesions and consequent narrowing of pneumothorax pocket. Last examination, made April 12, 1930, seven months after discontinuance of second

pneumothorax, showed no evidence of clinical activity. Patient stated that he had been on full-time work for last 15 months without experiencing any untoward effects. X-ray film, taken same date, confirmed patient's report and physical findings.

Case 2: B. R., male, age 22, occupation student, admitted July 25, 1926, with history of pulmonary tuberculosis of 3 years' duration and that pneumothorax on right side for control of haemoptysis had been initiated in another institution in September, 1925. Physical and roentgen-ray examinations disclosed fairly complete pneumothorax on right side and active infiltration of left upper lobe with well-defined apical cavitation. Clinical course characterized by daily temperature of 101°F., moderate dyspnoea, excessive cough and bacillary sputum, and intestinal symptoms characteristic of tuberculous enterocolitis. Owing to a report that there was cavity on right side between 2nd and 3rd

PLATE 1

Case 1

FIG. 1. Acute exudative tuberculosis of entire left lung.

FIG. 2. Two months after admission. Satisfactory compression of diseased lung.

FIG. 3. Twenty months later. Note acute exudative process in right lung.

FIG. 4. Six months after second admission. Showing complete reëxpansion of left lung and "selective" collapse of right lung.

FIG. 5. Three years later, 7 months after discontinuance of second pneumothorax and 5 years after onset of disease. Note complete reëxpansion of right lung. Patient has been on full-time work for 15 months with complete freedom from symptoms.

ribs, the advisability of reëxpanding that lung was considered problematical. Simultaneous bilateral compression was deemed inadvisable because of dyspnoea and intestinal complication. Watchful waiting was, therefore, considered safest course to pursue. It was decided, however, to decrease frequency and amount of air refills. In December, 1926, chest film showed nearly complete reëxpansion of right lung with no evidence of cavitation, and moderate clearing of the exudation below left apical cavity. As symptoms continued unabated, pneumothorax was instituted one month later on left side, resulting in a satisfactory "selective" collapse. Considerable improvement followed. Under dietetic regulation and heliotherapy, intestinal symptoms also subsided. Patient left hospital in June, 1928, in greatly improved condition, although he still raised daily about 2 cc. of bacillary sputum. Observation and treatment were continued in the out-patient department. In December, 1928, patient reported that he was entirely free from cough and expectoration, and rarely suffered any intestinal disturbances. In February, 1929, the second pneumothorax was discontinued on account of a pocketed

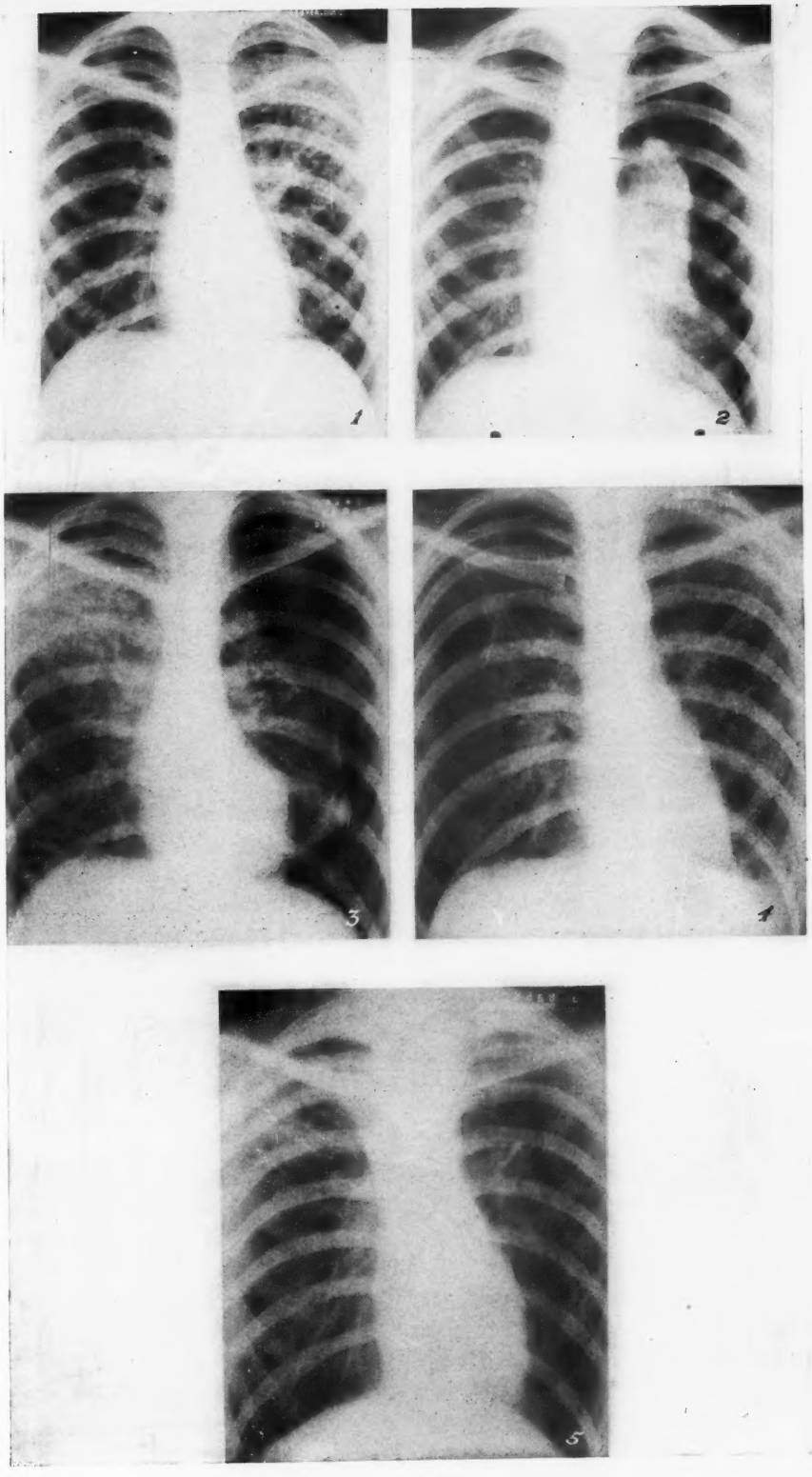

PLATE 1

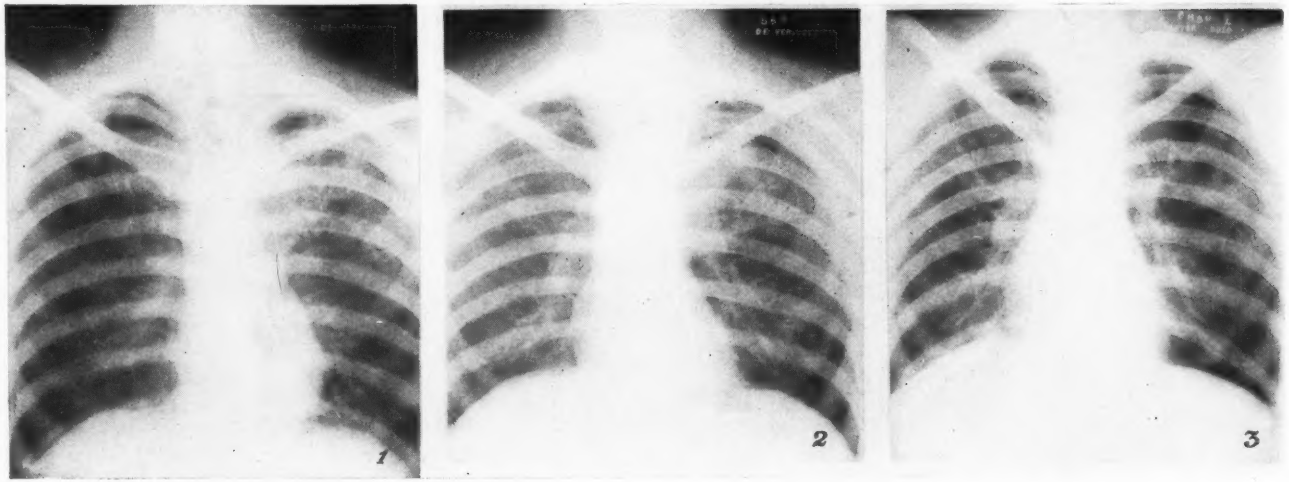

PLATE 2

Case 2

FIG. 1. Admission plate, showing right-sided pneumothorax of 10 months' duration with active infiltration and cavity-formation of left upper lobe.

FIG. 2. Seven months later. Complete reëxpansion of right lung and localized pneumothorax on left side.

FIG. 3. Twenty-nine months later. The second pneumothorax had to be discontinued on account of a pocketed effusion which caused obliteration of pleural space. The relative clearance of lesion on left side should be noted.

serous effusion. Last examination in July, 1929, showed that fluid had become completely absorbed. There was slight recurrence of intestinal symptoms, but there was no apparent active disease in lungs.

Case 3: H. K., female, age 20, occupation manicurist, admitted November 16, 1923, with history of pulmonary tuberculosis of 2 years' duration. Physical examination pointed to bilateral upper-lobe involvement. Chest film revealed well-defined cavity on right side at 2nd rib, with active inflammatory process extending to apex. Between 2nd and 4th ribs on left side there were noted small areas of scattered mottling. After 7 months of conservative treatment, during which there occurred some clearing on left side, right-sided pneumothorax was instituted and satisfactory collapse obtained. Corresponding clinical improvement followed, but bacillary sputum persisted, the source of which was suspected to be left lung, as right-sided cavity appeared completely compressed. In October, 1925, physical signs pointed to definite progression on left side and beginning cavitation. Although the pneumothorax initiated on right side had been of only 16 months' duration, a period considered too brief to cause closure and healing of a cavity, it was decided to gradually deflate that lung, for it was believed that the left-sided lesion could not possibly be controlled by a slight or partial lung immobilization; hence simultaneous compression of both sides was out of consideration. Chest film taken early in December showed fibrosis with no evidence of cavitation in the completely reëxpanded right lung, in contrast to definite cavitation on left side. Left-sided pneumothorax instituted in January, 1926, resulting eventually in complete compression of the cavity. Within 18 months from the time second pneumothorax was started, patient had gained 30 pounds, and sputum had become negative. Right lung gave signs of healed lesion. Patient returned to work in September, 1927, and enjoyed fair degree of health until January, 1929. A detailed report of her subsequent clinical course while patient in another institution could not be procured, except for note stating that immediate cause of death, which occurred in June, 1929, was a "spontaneous pneumothorax on the right and pneumonia on the left."

Case 4: L. L., age 23, male, occupation clerk, admitted June 20, 1924. Onset of present illness dated to January, 1921. On account of recurring haemoptyses, pneumothorax administered on right side in September, 1921. Chest film on admission showed satisfactory collapse of right lung, and active infiltration of left upper lobe. Subfebrile temperature, cough and bacillary sputum persisted. Symptoms attributed to ulcerative process in left lung, but, owing to associated tachycardia and moderate dyspnoea, simultaneous compression was deemed hazardous. Deflation of right lung considered unsafe, since the measure was instituted to control haemorrhage, and a record of the character

and extent of lesion prior to compression was not available. Clinical course apparently stationary until December, 1925, when brisk haemoptysis occurred. Physical examination and X-ray film proved that source of the bleeding was from left side. Right lung now permitted to reëxpand. When this process was completed, physical signs were those of healed lesion, but tracheal deviation to right and uniformly opaque apex, as seen on roentgenogram, constituted very suspicious evidence of cavitation. Nevertheless, pneumothorax on left side was instituted in July, 1926, in order to control there the active and progressive lesion. Marked improvement followed. At time of discharge in July, 1928, patient was free from symptoms except for small amount of bacillary sputum, rarely exceeding 10 cc. in 24 hours. As left lung was very well compressed, the source of the sputum was believed to be cavity at right apex, notwithstanding negative physical findings in that region. Rehospitalization became necessary in June, 1929, on account of haemoptysis. Physical examination at this time elicited many bubbling râles on right side from 2nd rib and 3rd dorsal spine up. X-ray film showed definite rarefaction at right apex and small pocketed effusion on left side. The latter complication made continuance of pneumothorax impossible. Patient's general condition now is satisfactory. Last examination made April 30, 1930, showed no apparent activity on left side. The small amount of air at apex simulates cavitation roentgenologically. There is unmistakable evidence of right-sided apical cavitation, for which surgical compression is being seriously considered.

Case 5: S. H., female, age 27, occupation housewife, admitted June 12, 1923, with history of pulmonary tuberculosis of only 3 months' duration. On account of extensive right-sided involvement with upper-lobe cavitation, pneumothorax successfully instituted three months later, after conclusion was reached that left upper-lobe lesion was inactive. Patient became ambulant and afebrile in February, 1924, and by end of December, 1924, being symptom-free, was discharged from the hospital with instructions to have refills continued. In June, 1928, she reported for examination. No evidence of pneumothorax, although patient insisted that she had been receiving refills every 2 weeks. Exploration of pleural cavity failed to find pleural space. Physical signs on right side those of healed lesion; left lung, with exception of slight changes in breath-sounds, disclosed no activity. Sputum negative. On readmission in April, 1929, on account of recurring haemoptyses during preceding 2 months, there was noted marked involvement of left upper lobe with large infraclavicular cavitation. No evidence of activity found on right side. Two hours after successful initial administration of 300 cc. of air into left pleural cavity, patient developed typical symptoms of spontaneous pneumothorax with marked visceral displacements to right, necessitating repeated withdrawal of air to relieve marked circulatory and respiratory embarrassments. Gradual

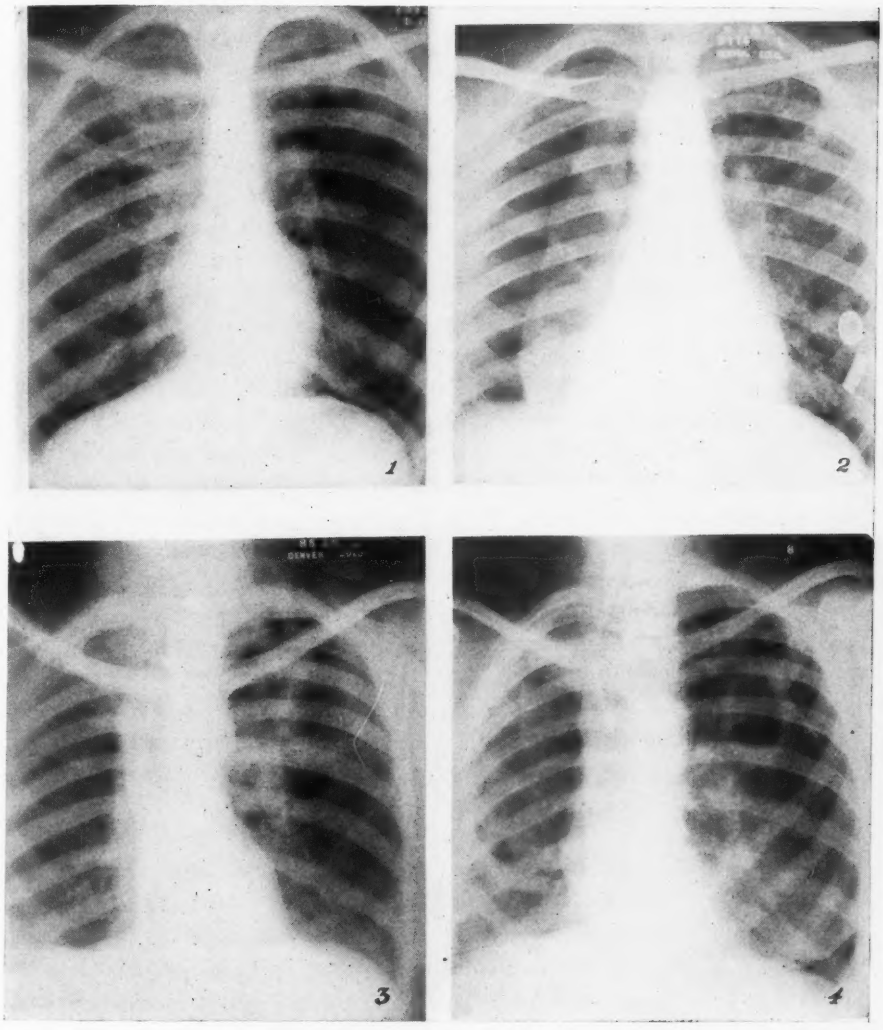

PLATE 3

Case 5

FIG. 1. Extensive involvement of entire right lung and apical infiltration on the left.

FIG. 2. Four months later, showing excellent compression of right lung with small amount of fluid at base.

FIG. 3. Six years after first admission. Note complete reëxpansion of right lung and large infraclavicular cavity in left lung.

FIG. 4. Six months after second readmission. The cavity could not be compressed by pneumothorax, and was the source of a fatal haemoptysis.

recovery followed and refills were continued. In September a large haemorrhage was controlled by refill of 700 cc. of air under positive pressure, although cavity remained uncollapsed. On November 30, patient had another haemorrhage, which proved fatal in a few minutes.

Case 6: J. K., male, age 24, occupation clerk, entered the hospital October 24, 1927. Duration of disease 5 years, and during last 3 years patient had been confined to bed in local sanatorium without improvement. *Principal Symptoms:* Cough, 20 to 30 cc. of purulent sputum daily, low-grade fever and progressive weakness. Physical and X-ray examinations pointed to bilateral, fibroulcerative lesion, involving greater portion of right lung and left upper lobe. First pneumothorax induced on right side on April 1, 1928. Partial collapse obtained, affecting only slightly upper lobe, where major activity was present. Nevertheless, X-ray film taken August 2, 1929, showed considerable clearing of infiltration on right side, and stethoscopic examination did not elicit any râles even over the uncompressed upper lobe. Three months later definite left-sided progression with cavitation was noted. On January 9, 1930, after the air in the right pleural cavity had become absorbed, 300 cc. of air were introduced into left pleural cavity. Refills have since been continued at regular intervals. An adhesion at 2nd rib anteriorly prevents satisfactory compression of small peripheral cavity, but clinically there is noted improvement. The patient has been ambulant and afebrile, has gained 8 pounds, and there is very little cough and only about 5 cc. of sputum. Prognosis still uncertain in view of persistence of bacilli in sputum, but, compared to condition before treatments were instituted, gains have been exceedingly gratifying.

SUMMARY AND CONCLUSIONS

Six patients with far-advanced pulmonary tuberculosis received alternating or successive pneumothorax and their clinical course was observed for two and one-half to seven years. In case 1, the indication was an acute contralateral involvement, 21 months after the first pneumothorax was instituted. The second pneumothorax was maintained for 26 months. The lesions on both sides were of the exudative variety, and the result was an apparent arrest of the disease. Case 2 developed a slowly progressive fibroulcerative process in the left lung, necessitating gradual reëxpansion of the right lung after 16 months of compression. The second pneumothorax was continued for 30 months, and, notwithstanding a coexistence of tuberculous enteritis, the pulmonary lesions seemed well fibrosed and apparently inactive. The 3rd case was afforded over 3 years of comparative well-being and usefulness by the institution

of left-sided pneumothorax after the right lung had been under compression for only 16 months. The extensiveness of the left-sided process with large cavitation could not possibly have been controlled by partial compression, which would have been the only safe expedient if simultaneous treatment had been attempted. The occurrence of spontaneous pneumothorax about 3 years after the right lung was reëxpanded is indeed a rare complication, since an obliteration of the pleural space is usually expected, but it is not altogether an uncommon experience to find in such conditions a pleural space when a reinstitution of pneumothorax becomes indicated. During the past 2 years we had such a pleasant surprise in 3 cases. It is therefore quite likely that in the case under consideration such an accident did occur and was the contributing factor to the fatal outcome. Case 4, after 6 years of a rather stormy clinical course with repeated haemoptyses, has now a chronic right-sided apical tuberculosis with cavitation, which is amenable to treatment by surgical methods. The recurrence of active disease on the right side 3 years after the pneumothorax was discontinued is indeed discouraging, in view of the fact that the first pneumothorax was maintained for 4 years and 10 months. It was because of that long duration that it was deemed safe to stop the treatment and institute compression on the left side for the control of a progressive lesion. The patient's general condition now, however, is good, and the left lung is clinically inactive. In case 5 the ultimate prognosis was unfavorable because of the noncompressibility of the left apical cavity, which was the source of frequent bleeding. This illustrates the inapplicability of simultaneous pneumothorax in such cases. Case 6 was selected primarily for alternating compression. The surprising fact was the marked clinical improvement of the right lung under slight and rather unsatisfactory compression. The incomplete left-sided pneumothorax is still maintained, and the patient is steadily improving.

A comparison of our results with those obtained by Rist and Chabaud (7) shows not only a reduction in the immediate and ultimate mortality in our series, but a cure in one case and an apparent cure in another case long after the discontinuance of the second pneumothorax. This verifies the prediction made by those authors of better results in the future from this procedure. The conclusion is, therefore, justified that many patients who develop contralateral disease during pneumothorax therapy, or have bilateral disease equally distributed, can be treated successfully by means of alternating pneumo-

thorax, and in some instances they may even accomplish a complete arrest of the disease.

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OLEOTHORAX

L. E. OPPENGAME[1]

Oleothorax, the injection of mineral or vegetable oil into the pleural cavity, is now a newly recognized procedure employed especially in France. The discussion of the indications, technique and results of this new therapeutic treatment should prove very interesting.

Briefly the indications are as follows: To avoid adhesions, to produce a more effective collapse when pneumothorax is unsuccessful, to give more rigidity to the pleura if a bulging of the mediastinum occurs, to close a perforation of the lung, to change an empyema into a sterile disinfectant oil and finally, in rare cases, when on account of social conditions a patient cannot continue with routine insufflations.

Statistics show that almost 70 per cent of pneumothorax treatments are complicated by pleurisies, 22 per cent of them undergo a transformation into empyema and, finally, as a result of adhesions following the absorption of the exudate, 15 per cent make further collapsotherapy impossible (J. Fontaine, *L'oleothorax,* Gaston Doin & Cie., Paris, 1929).

These unsatisfactory sequellae were always a weapon in the hands of adversaries of pneumothorax treatments. Why then do we continue this mode of therapy with the apparently bad results as the above mentioned statistics show? Mainly because not all pleurisies are intoxicating for patients, because a great number are beneficial for pulmonary tuberculous lesions and, lastly, because physicians with long-standing experience with pneumothorax work, are not discouraged by the first appearance of an effusion. Such patients improve considerably during a pleural effusion or immediately after it, and tuberculosis specialists not only avoid any interference in these, but consider their appearance as a natural healing and encouraging phenomenon.

It seems paradoxical that an effusion with tubercle bacilli should be beneficial for patients, but the striking experiments of Rist and his school explained this problem in a satisfactory way. They observed that an allergic exudate frequently does not infect a healthy guinea pig and also

[1] New York City.

that an allergic guinea pig does not contract peritoneal tuberculosis. Furthermore, Rist and Veber (*Annales de Médecine*, vol. 24, July, 1928) could not produce tuberculosis in animals in which they injected pleural fluid rich with tubercle bacilli from pneumothorax patients, and the numerous tubercle bacilli from such pleurisies do not grow on glycerin-potatoes or on Petroff's culture medium. Virulent tubercle bacilli from standard cultures, when mixed with pleural fluid from patients treated by pneumothorax and placed in thermostats for a certain time, are not able to grow if replaced on favorable media. Such virulent tubercle bacilli, after the contact with pleural fluid, change their known morphological forms; their color becomes abnormal and they become granular, all of which proves the transformation and death of the bacilli.

From a scientific point of view such pleurisies are interesting, but certainly not all pleurisies are very benign, and we must not forget the existence of very intoxicating grave pleurisies, which are fatal for patients and some other pleurisies which stand between both limits. Dumarest has classified pleurisies into the following groups:

Tolerated Pleurisies: Little torpid precocious effusions. Only fluoroscopy or X-ray films permit us to discover these small pleurisies, mainly filling up the costophrenic angle and not progressing. These patients have no fever or pain. They are idiopathic silent forms, produced by trauma of the pleura, say Dumarest and Parodi, or simple pleural serosities formed as a result of irritation of the pleural membranes from the insufflation, as explained by Rist and Veber. No treatment is necessary in such cases. The reabsorption occurs sometimes by itself, but precaution must be taken in further insufflations.

Acute Febrile Effusions (*serofibrinous*): These frequently appear between the 3rd and 5th month, but may also occur at any time of pneumothorax treatment. They are enormous effusions, which we see often also without a pneumothorax treatment, characterized by severe chills, high fever, a stitch in the affected side, marked dyspnoea, irregularity of the pulse, and increased expectoration and cough. In the first phase the effusion reaches in several days up to the clavicle. The temperature is high. In the second phase the effusion is stationary, the fever recedes and all acute symptoms become more quiescent. In the third phase a regression of the effusion is marked and it can either partially or completely disappear. The temperature is normal. Very often a small effusion may persist for months or even years and not interfere with the pneumothorax treatments. The transformation of such pleurisies into an em-

pyema is not an uncommon occurrence. They are mostly benign, often regressing or disappearing when air refills are discontinued. Subsequently, however, they often give more or less adhesions. Certainly such pleurisies after any secondary infection (tonsillitis, influenza) undergo a malignant transformation. Then the prognosis is very grave.

In all the above-mentioned pleurisies an oleothorax does not come into consideration, except possibly to prevent adhesions. In contrast to these acute or subacute effusions, an oleothorax also has the disadvantage of casting very dense shadows on X-rays, making detailed study of the case difficult. Due to the considerable absorption of oil, refills with resultant pleural trauma constitute an unavoidable factor. Therefore in such effusions, after the acute stage is over, we follow the advice of J. Fontaine and others, aspirating the fluid and refilling with air, abstaining from oleothorax.

Malignant Pleurisies: Serofibrinous or purulent, are chronic effusions with high and prolonged fever and of a severe character, causing malnutrition, says Küss. Such pleurisies may develop from the above-mentioned, and the difference between them is not easy to recognize at once; only the evolution of the disease permits one to differentiate the two forms. Such malignant pleurisies are mostly fatal, and the rare cases described by some writers as cured must be considered as localized suppurations but not generalized empyemata.

The end-result of these kinds of pleurisies is a complete prostration or amyloid degeneration. The multiple pathological possibilities of such pleurisies cannot be discussed in this paper, but to demonstrate the importance of differentiation of some of them it may be mentioned that an empyema of pleural origin is less severe than a suppuration produced by an opening of a cavitation into the pleural space, and, as we know, such perforations are mostly recognized postmortem, but not clinically nor by manometric readings.

Statistics show only 10 per cent to 12 per cent of empyemata complicating pneumothorax treatments, with a mortality of 85 per cent. In 48 per cent thickening and adhesions occur, and in 37 per cent death by complications, such as lung perforations, fistula, etc. (J. Fontaine).

Fiessinger and Lemaire (*Presse Médical, February, 1926*) tried to inject lipiodol after aspiration of such empyemata, but the results were disastrous; also argyrol and electrargol were tried by others without success. Besançon and Etchegoin obtained better results by injecting codliver oil. Our own experience is limited to injections of mineral and

vegetable oil; that is why the following discussion of oleothorax includes only the two kinds of oil,—olive and paraffine oil.

With rare exceptions, as we said, there is no use for oleothorax in benign pleurisies; but in malignant cases the first step in any intervention is an oleothorax. Even if the latter is unsuccessful, you enable the patients better to withstand further surgical interference, such as rib-resection, thoracoplastic operation, etc., as an oleothorax, without question, improves the general condition of patients. Certainly the procedure of choice in nontuberculous primary empyema permits of discussion, says Burnand; but an empyema complicating an artificial pneumothorax, which means that we have to deal not only with a pleurisy, but with tuberculous lesions as well, has only one choice, an oleothorax, as a thoracotomy is almost fatal for such patients. In general, all tuberculous pleurisies should be treated by oleothorax, as rib-resection gives a persistent fistula, which never ceases to drain. Only a thoracoplasty is able to help, but the results are not encouraging; besides, an oleothorax if properly and well done, is entirely harmless.

Some authors claim that good results are obtained by simple aspiration of such malignant pleurisies, but the majority are sceptical about the striking results. None of these writers state in the classification of such pyopneumothoraces whether they are febrile or afebrile.

Secondarily infected pleurisies may be treated by means of drainage if produced by streptococci or pneumococci. Only a tuberculous pleurisy is suitable for an oleothorax.

The use of oleothorax in lung perforation is very limited. A small perforation, as a result of the breaking of adhesions, or a rupture into the pleural cavity of a small subcortical vomica, not connected with a bronchus, justifies an oleothorax. Unfortunately, not very often are we able to differentiate the small benign perforation from a large fatal one. Burnand (*La perforation du poumon, Annales de Médecine*, xi, no. 1, 1921) classifies them into the temporary benign perforation and the permanent large open perforation and the valvular perforation. Without or with any alarming symptoms, the temporary perforations are mostly discovered by manometric readings, or by pulmonary lobar atelectasis seen on fluoroscopy. The valvular perforation, known by clinicians as a suffocating pneumothorax, has the typical symptoms of dyspnoea, point pain, hippocratic facies, positive manometric readings, and collapse of the lungs if the air escapes into the pleura, but, if the air goes from the pleural cavity into the lung, which Bernou calls an inverse

valve, then the pressure is negative in spite of refills and the lung has a tendency to reëxpand.

The temporary perforation does not need an oleothorax, for the symptoms very often retrogress in a short time. For the valvular perforation a permanent deflation is sometimes a great help, but, if the alarming symptoms persist, an oleothorax is indicated, especially since an empyema practically always results from such perforations. The large perforations are mostly fatal. But if the large perforation is unilateral and recognized at once, an immediate thoracoplastic operation is a help. Nevertheless Burnand and Roussel injected oil in such cases, especially if a suppuration followed a pneumothorax. They thereby disinfected the pleura, improved the general condition of the patients, and placed them in such condition that patients were more resistant for a final thoracoplastic operation. Even after the operation they treated the persistent suppuration by gomenol-oil injections.

In adhesions the only treatment was a surgical treatment: thoracoplastic operation in large adhesions and a Jacobaeus procedure in small ones. Bernou was the first to show that with an oleothorax we may avoid and prevent adhesions. Of course, not all adhesions need an immediate performance of an oleothorax. Pleural lesions, transformed into adhesions and situated far from a subcortical pulmonary lesion, may be considered a favorable transformation; also adhesions occurring at the site of a small rupture.

It is very important to foresee the beginning of adhesions; the best indication is given by manometric readings. If, for instance, at the beginning of a refill a higher pressure than at the end of the previous insufflation occurs, then the possibility of adhesions must be ruled out. Such abnormal readings are also possible in the beginning of a pleurisy, when the quantity of fluid is increasing, or in a long-standing pleurisy, when the rigidity of the pleura and the diminished reabsorption of fluid causes such a high pressure and abnormal manometric readings. In these cases fluoroscopy is the best means for a differential diagnosis.

In unsuccessful pneumothorax, for instance, in partial pneumothorax, when only one part is collapsed far from a cavitation which remains open, Küss advised in 1925 an oleothorax, as insufflations are not only useless, but dangerous, because of the necessary high pressure.

Also, the mediastinal hernia or bulging produced by low pressure on the opposite side of a pneumothorax may be reduced by an oleothorax. After several months of maintaining an oleothorax, such a weak medias-

tinal pleura becomes fixed and then a complete blockage with oil of the hemithorax is possible. In these cases Bernou advises the injection of small quantities and, when bulging has receded, to perform a complete blockage.

Finally, in rare cases and exceptionally if patients are not able to stay in the hospital or to be refilled in dispensaries, a pneumothorax may be changed into an oleothorax, which requires refills only every two to three months.

To determine and to limit the indications of an oleothorax, we agree with the resumé given by Jacqueline Fontaine:

A: An oleothorax must be done without hesitation:

1: In either primary tuberculous empyema, febrile pleurisies, chronic simple pleurisies, or as the consequence of an artificial pneumothorax. In such cases an oleothorax cures; if not, it is useful as preparation for a thoracoplastic operation.

2: In pulmonary perforations with persistent valve or accompanied by purulent pleurisies.

3: In cases of progressive adhesions, which are menacing the necessary collapsotherapy.

B: The oleothorax should be considered:

1: In serous pleurisies produced by pneumothorax treatments, if they are febrile, recurring, and if accompanied by impaired general condition.

2: In large open perforations, as a preparation for a thoracoplastic operation, if the general condition does not permit immediate surgical interference.

3: To replace certain unsatisfactory pneumothoraces.

4: In exceptional cases in which pneumothorax refills are not possible.

Here are some cases and indications of oleothoraces performed in Sea View Hospital:

Case 1: Miss S. S., age 38, nurse, admitted June 1, 1929. *Admission Diagnosis:* Chronic pulmonary tuberculosis (Dr. Lloyd). *Left Lung:* movement limited, many râles throughout the lung from apex to base. Amphoric breathing at second intercostal space anteriorly and second d.s. posteriorly (cavitation). *May 31, 1929:* Initial pneumothorax.

X-Ray Report (June 17, 1929): Pneumothorax at left, from apex to base, string adhesions at fourth rib and diaphragm, small amount of fluid in costophrenic angle. Two large cavities still open with fluid levels (Dr. Lloyd), temperature 98°–99°. *Sputum* (May 24, 1929): Tubercle bacilli numerous. Expectoration, 2–4 boxes per 24 hours.

On October 18, 1929, patient developed pleurisy and the manometric reading after 50 cc. of air was $-\frac{1}{2}$, $+4$. As it was a benign pleurisy we left it until January 10, 1930, when the beginning of pleural thickening was evident: the manometric reading after 50 cc. of air was $+2$, $+4$. The cavitations were still open. Patient expectorated about the same quantity of sputum as before the pneumothorax treatments and ran the same temperature,—98°–99°.

An oleothorax was performed. Ten cubic centimetres of mineral oil with gomenol injected (January 10, 1930). Patient did not react to the injection: no elevation of temperature, no malaise. *January 13, 1930:* Injected 120 cc. of oil. *January 20, 1930:* Manometric reading, -6, $-\frac{1}{2}$; 85 cc. of oil-gomenol injected. *January 27, 1930*: After 100 cc. of air, -3, -0; 125 cc. of oil injected. Until October 1, 1930 patient had in all 970 cc. of oil-gomenol.

The patient is now afebrile, has no expectoration, and only once a small amount of sputum was obtainable (March 6, 1930) which was negative for acid-fast bacilli. Patient gained 6 lbs.

This case is an illustration of an oleothorax first performed by Küss in 1925 only on account of adhesions: if air is not sufficient to collapse a lung with cavitations on account of adhesions, oil, being more compressive, is indicated.

Oil was also necessary in this case on account of thickening of the pleura, following an effusion. It was just the time to perform an oleothorax, as the manometric reading on January 10, 1930, ($+2$, $+4$) was higher than the reading on the previous insufflation, indicating that the fluid was absorbed. This was proved by aspiration, a dry pleural tap being obtained.

The patient is now clinically almost cured, no pathological symptoms being present. As a curiosity, we mention in this case oil tumors, which developed on both legs, similar to paraffinomata. They disappeared after 3 to 4 months, only ammoniate of mercury having been applied. Anyhow, we must warn against the use of mineral oil, as in the French literature one case of real mediastinal paraffinoma is reported (unfortunately without mention of the issue of this case). The more harmless olive-oil injections will probably be used in the future. This case illustrates also the combination of a pneumothorax and oleothorax: after several oil injections the readings changed from positive to negative, because the oil mechanically separated the visceral and parietal pleurae and avoided an obliteration of the pleural space.

Case 2: Miss A. B., age 21, admitted July 29, 1929. *Diagnosis:* Chronic pulmonary tuberculosis. *X-ray Report:* Bronchopneumonic type of pulmonary tuberculosis, mainly unilateral. *Left Lung:* Diffuse involvement of entire lung with multiple cavities in upper lobe. *Right Lung:* Negative, except for some hazy appearance at apex and increased size of hilar lymph nodes (?); lower bronchial roots somewhat prominent.

January 30, 1930: Initial pneumothorax (400 cc., -4, -1). *February 20,*

1930: After several refills, reëxamination of the chest shows left sided hydropneumothorax, with fluid level up to 3rd interspace and displacement of mediastinum and trachea to the right. In the region of the left upper lobe is seen some lung tissue, with well defined and sharply demarcated areas of lessened density which are undoubtedly uncollapsed vomicae held by adhesions to the chest-wall.

February 24, 1930: Lemon-colored fluid aspirated from left chest (500 cc.); 30 cc. of oil-gomenol injected; normal reaction. Patient had in 4- to 6-day intervals several injections until complete blockage was obtained by June 30, 1930. Since the last injection we control the amount of oil once every four weeks. The reabsorption of oil in this case since a blockage was obtained was very slow, and we injected only 5 to 10 cc. of oil once a month. This case is particularly interesting. Why did we change an acute febrile effusion into an oleothorax and what effect was obtained by an oleothorax? Because in spite of the effusion the cavitations in the upper lobe were open on account of adhesions and because a menacing mediastinal hernia (bulging) occurred which interfered with the further pneumothorax insufflation. After 2-3 months of oil treatments we obtained a rigidity of the mediastinal pleura, the hernia disappeared, and we were able to inject a considerable amount of oil without fear of rupture. In the meantime the patient developed after a pneumonia a right-sided pulmonary lesion. We feared to perform a right-sided pneumothorax on account of the left-sided oleothorax, and decided to inject sanocrysin intravenously. The patient is now in a very good condition.

Case 3: Mrs. I. B., age 40, admitted July 27, 1929. *Diagnosis:* Chronic pulmonary tuberculosis. X-ray report: Artificial pneumothorax at left, upper lobe, which shows a cavity not altogether collapsed, held by adhesions to chest-wall. Costophrenic angle obliterated and slight amount of fluid present.

This case is identical to the previous one. We performed an oleothorax, on account of adhesions, uncollapsed cavity at the apex and thickened pleura. The interesting part of it is that after six months of an oleothorax, during which the patient was in a very good condition, she began to run an evening elevation of temperature and her general condition became impaired. The control of oil in the subclavicular region was absolutely normal: pure oil by aspiration was obtained. But in the 7th intercostal space in the axillary line we obtained a purulent fluid. Changing this suppuration into a sterile oil-gomenol fluid, the temperature dropped to normal in 24 hours and the patient is now still in a pretty good condition.

Case 4: Miss C. C., age 16, admitted April 29, 1929. *Diagnosis:* Chronic pulmonary tuberculosis; scoliosis of spine; syphilis (Wassermann ++++) (Dr. Buchman). *X-Ray Report:* Exudative tuberculosis in left upper lobe

and cirrhosis on same side with displacement of heart. Moderate scoliosis with convexity toward the right (Dr. Stoloff).

August 28, 1930: Initial pneumothorax (200 cc. of air: —2, +1). The artificial pneumothorax in this case was unsuccessful on account of many adhesions. *September 28, 1930:* Patient has been streaking rather moderately for past week, during which she has been confined strictly to bed and received the routine treatment. *Physical Examination:* Only moderate amount of moisture in left side. For past two days patient has had subfebrile temperature, increase of cough and night-sweats, suggesting some pneumonic spread of sequellae of this haemoptysis. Pneumothorax withheld in this interval. Surgical procedure necessary, probably phrenicotomy preparatory to thoracoplasty (Dr. Kovnat). Patient in very bad condition. Oil-gomenol advised and 20 cc. injected. The pleural reaction was normal, but patient spat up the oil. A bronchopleural fistula was evidenced. Now an oleothorax was desirable, not only as a more compressive treatment, but to close a small rupture. This was obtained after injection of 500 cc. of oil. Up to the present time (December 26, 1930) patient has had 2800 cc. of oil-gomenol and a complete blockage is now obtained. No further pulmonary haemorrhages reported. Patient has a well-collapsed left lung and her general condition is excellent. The bronchopleural fistula is closed.

This case is interesting because of the enormous ability of the pleura to absorb mineral oil. In general the pleura absorbs more vegetable oil than mineral; this is why vegetable oil with gomenol is preferably used in empyemata, because by such a rapid absorption the function of liberated gomenol as an antiseptic is more desirable for the infected pleura. Such an interpretation was given in the beginning of oleothorax treatments by Bernou. He also used exclusively vegetable oil because of the ease of procuring such oil for the treatments. Now we believe more in the mechanical action of an oleothorax than in it as an antiseptic; that is why Küss and others use more mineral oil, which is less absorbed than vegetable oil by the pleura, and the stability, conservation and the preparation of this oil are much easier than in the case of vegetable oil.

Many accidents occurred from injection of badly and anciently prepared, not neutralized vegetable oil, but, if all necessary precautions are taken in the preparation of both oils, no great difference is attached now to the choice of the oil used. It seems that the power of reabsorption depends more on the individual patient than the kind of oil. Anyhow, the vegetable oil is milder for the pleura and not so irritant as the mineral oil. We are using the latter in cases to avoid thickening of the pleura and to produce more compression; the vegetable oil we are using mostly in empyemata.

We give the more striking cases in the use of oleothorax as examples. For the last six years we have treated and observed many patients and we have not had one death directly from a performed oleothorax. We believe that the reported cases of death after oleothorax treatments are due to the neglect by physicians of the pressure which oil produces. The measure of pressure by an oleothorax is the most important factor. The pressure of air above the oil level is very easy to control with the water manometer of a pneumothorax apparatus, but the pressure developed from oil on the pleural wall is very difficult to measure. The metallic water manometer which Bernou uses for this purpose and the oil manometer used by Küss are not absolutely precise. The difference in readings in using the two manometers in the same patients is very great; this is why the use of it to-day is very limited. Experience with this matter is a great help.

OLEOTHORAX

PAUL DUFAULT[1]

Oleothorax is a therapeutic method which consists of the introduction of a considerable quantity of antiseptic or aseptic oil into the pleural cavity.

The idea of injecting oil into serous cavities goes back to 1906, when Wegner and Recklinghausen demonstrated that oil occludes temporarily the capillaries of the peritoneum. In the same year Glimm published the results of his experiments on the resorption of oil in the peritoneal cavity. In 1912 numerous other workers (particularly Peiser, Hirsche and Arnault) injected camphorated oil into the peritoneum with the idea of preventing the formation of adhesions.

In 1915 Burnand introduced a small quantity of oil containing a certain percentage of gomenol into a pyothorax. In 1916 Fournier of Bordeaux recommended gomenol in oil to shorten the duration of cases of serofibrinous pleurisy. In 1918 more workers were investigating the subject. P. E. Weil and Loisseleur used gomenol in oil in the treatment of tuberculous pyopneumothorax, and Cordier and Hinault tried to prevent pleural adhesions by the same means. In 1922 Bernou introduced the largest quantity of oil yet injected into the pleural cavity, and called the method *Oleothorax*. In the same year a few observations demonstrating the effectiveness of oil-injections as a preventive for adhesions were published by Moigneteau. Thin, in his thesis published in 1923, recognized the antiseptic and antiobliterative powers of oleothorax.

It was not long, however, before some writers and observers condemned the practice of oleothorax as ineffective or dangerous. Numerous reports and observations were published of complete failures or deplorable accidents. The method was recognized by others as valuable only in some of its indications and as absolutely worthless in all the others.

We owe to such an authority as Küss a masterly summary of the indications and technique of oleothorax (*Revue de la tuberculose*, February,

[1] Rutland State Sanatorium, Rutland, Massachusetts.

1926). During the past few years a vast bibliography on the subject has appeared in the French, Italian and Swiss literaturre. Oleothorax has been endorsed by such men as Dumarest, Rist and Bezançon. There is no book on pneumothorax which does not devote a chapter to oleothorax.

In this country the method has been mostly ignored or criticized. In May, 1927, J. N. Hayes reported, without much enthusiasm, two cases of bronchial fistula and one case of haemorrhagic pleurisy, all treated by oleothorax.

I shall summarize briefly the chief indications of oleothorax, and also report two cases in which its application as a palliative measure was rather encouraging.

The use of oleothorax is advocated in pleurisies, in pleuropulmonary perforations, as a preventive against progressive adhesions, and as a means of compression.

PLEURISIES

The pleurisies may be divided into two groups: (1) the tolerated pleurisies and (2) the severe pleurisies.

The first group includes all the exudates appearing so frequently during the first months of therapeutic collapse and (in most instances) resorbing spontaneously. Aspiration of the fluid and refills with air are the preferred interventions whenever the functional symptoms necessitate any active therapeutic measure.

The severe pleurisies may be such from the start, or may result from the transformation of the preceding type. They constitute an altogether different problem. Küss subdivides them into two types: (1) the recurring type of exudate with a tendency to reappear in spite of repeated tappings and accompanied by persistent fever, and (2) the secondarily infected bacillary pleurisy.

In regard to the first type, Küss says:

> The lung should not be allowed to macerate in bacillary pus, which favors softening of cortical tubercles and pulmonary perforation. The oil blockage of the pleural cavity is the best method to assure prolonged compression and to heal subjacent lesions, exerting at the same time an antiseptic action without causing any harm.

In regard to the secondarily infected bacillary pleurisies, he claims that "Remarkable results have been obtained in serious cases with antiseptic oleothorax by Bernou, Burnand, Bezançon, Rossel and others."

PERFORATIONS

The main causes of pleuropulmonary perforations are the rupture of adhesions at their points of attachment on the visceral pleura and the breaking of a tubercle through the pleura. The actual wound inflicted by a trocar on a healthy pleura has very little importance and may practically be neglected.

Dr. Fontaine in her thesis divides perforations into 4 groups: (1) The small, temporary perforations; (2) the check-valve type of perforation, in which the air passes from the lung into the pleural cavity, or, less frequently, from the pleural cavity into the bronchus; (3) the large and permanent perforations; and (4) the perforations with intermittent manifestations.

The small perforations are most of the time symptomless and impossible to detect even by manometric readings. Only on the spontaneous collapse of the pulmonary stump can they be suspected. The explanation seems to be that such perforations are not in connection with a bronchus. They usually heal spontaneously.

Oleothorax is recommended for the valvular type of perforation, especially if complicated by the presence of an effusion, as is often the case.

The weight of oil, by immobilizing the lung, will give the fistula a chance to heal, and at the same time dry up the pleural cavity. This condition, untreated, would lead to asphyxia or decompression.

Oleothorax is usually contraindicated in a case of large gaping perforation. Thoracoplasty must be resorted to if the contralateral lung and the general condition warrant it. If the patient is unable to stand the operation, or if the contralateral lung is affected, external drainage is suggested as a preparation for surgery. Bernou and Rossel claim that oleothorax can be used with advantage and have reported a successful thoracoplasty prepared for by an oleothorax. The suppuration persisting after the operation was treated and cured by another oleothorax.

ADHESIONS

Adhesions are greatly favored by pleural effusions and frequently follow them. They may appear, however, on a dry pleura despite all

efforts of the clinician to prevent their formation and progress. We are all familiar with the various processes of ascending or descending adhesions, progressing upward or downward between the visceral and the parietal layers of the pleura, and leading more or less rapidly to complete obliteration of the pleural cavity. Membranous partitions, subdividing the cavity into small pockets, are by no means a rare occurrence. Dumarest reports a case in which the presence of an effusion rich in fibrin favored the formation of a band of adhesion between the diaphragm and the base of the upper lobe. Bernou concludes from a study of the pleural fluid-content that "All fluid forming a fibrinous mass within a few minutes of the withdrawal must be carefully watched, because it is in process of active resorption and is susceptible to form adhesions." Dumarest points out a notable increase of fibrin in the fluid when in process of resorption. Effusion, however, is not the only factor responsible for pleural adhesions. All those familiar with the practice of pneumothorax know the many deceptions encountered in the course of their daily work. In the selective collapses a delay of a few days is sufficient to allow a contact between the parietal and the visceral layers of the pleura and thus to create an adhesion. The partial collapses which comprise the great majority of all pneumothoraces have usually a marked tendency to close, in spite of careful refills.

In a survey conducted by the American Sanatorium Association on reëxpanded pneumothoraces, to which survey we are contributing our own cases, I was deeply impressed by the predominance of pleural adhesions, which account for the greatest majority of failures, and which are responsible in most instances for early discontinuance of the treatment.

The patient's outlook when pleural obliteration forces the operator out depends largely on the nature and extent of the lesions in the collapsed lung. If further compression is considered necessary, none of the means at our disposal should be neglected to obtain it. Oleothorax seems to have here a very proper indication.

It should be started at the first threat of any reaction in the fluid present in a partial pneumothorax; otherwise the possibility of maintaining an effective collapse is greatly compromised.

Adhesions forming in a large pleural cavity must be watched closely, and the pressure should be carefully increased. But if, in spite of higher pressure, those adhesions progress rapidly, oleothorax should be resorted to without delay. Its mechanical action will keep apart the visceral and parietal pleurae.

COMPRESSION

Küss brought to the attention of the French Academy of Medicine in 1925 the fact that the powerful and permanent action of oil-blocking can effect a good compression of tuberculous lesions, especially cavities in cases in which pneumothorax is ineffective.

The ineffectiveness of the collapse may also be due to an exaggerated elasticity of the pleura or to laxity of the mediastinum. Small quantities of gomenol in oil are usually sufficient to thicken the pleura and tie the mediastinum in forming partial adhesions. After that result has been obtained, air-refills may be resumed and an effective degree of collapse obtained.

One cannot avoid being impressed by the importance oleothorax occupies in the active treatment of pulmonary tuberculosis in various European clinics. It is hardly conceivable that such universally recognized masters as Rist, Küss, Bezançon and Dumarest would adopt and use a method either dangerous or of no avail.

Granted that its application may be limited to a few well-chosen cases, granted also that its results may often be but palliative in nature, should it not yet be assigned a place among our other means of collapsotherapy? In the phthisiologist's armory all the weapons are not of equal value, nor is each one as frequently used as another. And, in the war we are waging, can any single weapon be safely discarded?

Case Records

Case 1: C. S., male, aged 47, entered the Rutland State Sanatorium on April 4, 1930. Had been tapped for wet pleurisy 12 years ago. In November, 1926, was in hospital 10 weeks for severe cold. Was transferred to a sanatorium from which discharged at own request after 4 weeks' residence. Coughing and raising during past 3 years. In November, 1929, while at work felt sudden sharp pain in right chest and had to give up work immediately. Consulted physician and was advised to go to a sanatorium. While awaiting admission, patient remained at home, mostly in bed. During this time,—November, 1929, to the date of his admission to the Rutland State Sanatorium,—cough increased and patient lost weight and strength. On admission, chief complaints were cough, abundant expectoration (8 oz. in 24 hours) and pains in right chest. Looked very sick, very weak, and almost emaciated. Temperature 101°, pulse 105, and respirations 22.

Chest Examination: Right Lung: Flatness at base and hyperresonance in axilla and below clavicle. No breath-sounds over area of dulness; amphoric breathing below clavicle and at level of 3rd and 4th dorsal vertebrae between

the spine and scapula. *Left Lung:* Resonance normal. Many medium and fine râles from 6th dorsal spine and the 4th rib upward. *X-ray Report: Right Lung:* Bony thorax markedly depressed. Pericardium and trachea pulled to right. Hydropneumothorax. Level of fluid reaches 3rd sternocostal cartilage. *Left Lung:* Infiltrated throughout.

As revealed by the history, examination and X-ray, we have a case of chronic pulmonary tuberculosis complicated by pyopneumothorax and pleuro-pulmonary perforation.

It is to be noted that the patient is in very poor condition, already emaciated and deeply intoxicated. The so called good lung is infiltrated throughout. Thoracoplasty cannot be considered on account of the general condition and the contralateral lung.

Is there any palliative measure which could give the patient a chance, even remote, or at least relieve his symptoms?

Oleothorax, already used in such cases, seemed to be the only answer to the problem.

The pleural cavity was emptied of its pus as completely as possible and washed with saline solution, and four hundred cc. of olive oil, to which 4 per cent of gomenol had been added, were injected into the pleural cavity. The patient felt immediate relief. He hardly coughed at all during the night, and he raised very little sputum compared to the amount he raised before the intervention. The temperature came down from 100.8° to 99.2° and remained around that mark for 4 days (it had been oscillating between 101° and 103° up to then). By this time the pus had formed again in large quantity as shown by percussion and X-ray. The same procedure, that is, withdrawal of pus and injection of from 400 to 800 cc. of gomenol in oil, was repeated four times at intervals of 5 to 8 days, always with the same results.

The patient was relieved of his cough and his expectoration; he felt generally better and could sleep perfectly well. The fever, however, remained high, and the patient gradually failed, and died (as was expected) on the 48th day after his admission.

Case 2: Sophie B., female, 22, unmarried, entered Rutland State Sanatorium in June, 1929. Had been coughing and raising as much as 4 oz. of sputum in 24 hours for 6 months previous to admission. Was very poorly nourished; had lost 27 lbs. since January of same year. Many coarse râles over entire left lung. Amphoric breathing heard below left clavicle. Only a few fine râles heard at right apex. X-ray film confirmed physical findings.

The case was considered suitable for collapsotherapy. Pneumothorax was started, and the patient improved remarkably. Sputum decreased from 4 oz. to 1 oz. in course of first month. Weight rose gradually from 92 to 114 lbs. within first 6 months of treatment. Temperature soon fell to normal; pulse remained high.

Six weeks after first inflation, fluid appeared, and the pleural cavity was soon filled. Tapping was repeated three times because the abundance of fluid caused mediastinal displacement and dyspnoea. The fluid withdrawn was a thin yellowish pus, in which numerous tubercle bacilli were found. The fluid was under pressure. The mediastinum resumed its normal position and the dyspnoea disappeared.

The contralateral lung, already slightly infiltrated, began to show signs of progression at the time fluid appeared.

On March 13, while lying on her healthy side, patient raised a considerable quantity of pus similar to that of the tapping. The accident was probably caused by a pleuropulmonary perforation. The diagnosis was confirmed by a fluoroscopic examination, which revealed considerable displacement of the mediastinum toward the contralateral lung, and by a manometric reading which gave a pressure of +4, +3. The pressure was brought down to 0. In spite of frequent air-withdrawals, there was a considerable displacement of the mediastinum, and at every insertion of the needle the pressure was +4 or +5 on the water manometer. The fluid also kept forming slowly and had to be aspirated.

In an attempt to disinfect the pleura and to give the perforation a chance to heal, oleothorax was instituted in the usual way, June 11, 1930. The pus was aspirated as completely as possible and the pleural cavity washed with saline solution; 50 cc. of oil of gomenol were injected. During the following days, 100 cc. and then 300 cc. of oil of gomenol were added. Patient felt comfortable. Air had still to be withdrawn, but at longer intervals, and pus-formation ceased completely, as indicated by the oil-level which remained the same from June 15 to September.

The patient gradually failed, and died about the middle of September, 1930.

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THE HEALING OF TUBERCULOUS CAVITIES

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Some time ago our attention was called to an article in the *American Journal of Roentgenology*, December, 1928, in which Pinner (1) quotes Graeff's statement, made in 1921, that the tuberculous cavity is the death-sentence of the bearer. He was inclined to agree with Graeff and stated that only a small minority of cavities closed. Graeff also believed that there was so little hope for those having well-marked tuberculous cavities that they should be excluded from sanatoria.[2]

As we have been studying serial roentgenograms of our patients to determine their progress for several years, the statements made seemed to be so greatly at variance with our experience that we decided, by a study of our records, to find if the prognosis of our tuberculous patients with cavities was as grave as stated.

If it is true that only a small percentage of cavities heal by rest therapy,[3] then we should waste no time in resorting to pneumothorax or other surgical procedures to eradicate these cavities at once, as they are always a constant danger, sooner or later leading to fatal haemorrhage, or spread of the infection by contiguity or canaliculization or the blood-stream. Also, if the patient lives long enough, amyloid changes and fatty degeneration of the viscera are very apt to occur.

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[2] It should be noted here that although these authorities have made the statements as indicated, they have presented little evidence to prove their contentions. Furthermore, in reviewing the literature we have found no one who has made report of investigations as to the healing of cavities.

[3] In order to attain the best results in the healing of cavities, rest treatment must be efficiently carried out. The patient's temperature is no longer considered the only barometer as to how much rest should be taken. Much more important is the lung pathological process, as revealed by the roentgen-ray and physical findings. All patients with cavities are required to rest in bed not less than twenty hours daily; some twenty-two or twenty-three, although many of these have a normal pulse and temperature. The maximum amount of freedom allowed is bath room, toilet, and dining room privileges, and to go to a show twice weekly in the immediate vicinity. Passes and furloughs are not allowed except for very urgent reasons. The purpose of this regimen is evident. Excessive activity, by causing increased respiration and expansion of the chest, is inimical to contraction and healing, and may even lead to extension of the tuberculous process.

In our consideration of cavities, we have relied on our roentgen-ray studies almost entirely. Physical examination we considered of no value, as only about 20 per cent of all cavities show the recognized physical signs (2). Positive sputum is usually present in cavitation cases and very often disappears when cavities heal, but there are too many exceptions to make it reliable.

In all our cases stereoroentgenograms have been studied at three months' intervals. Cavities have been diagnosed by annular shadows and diminished opacity. In our interpretation of annular shadows, we have followed the dictum of Bruns (3), Burnham and Brown (4), and other clinicians, that all annular shadows should be considered cavities unless proved otherwise. Indeed, nearly all leading phthisiologists agree with the above method of interpretation, and it is rare that a dissenting voice is heard.

In regard to our material for study, it was stated above that it has been the custom to take stereoroentgenograms of all patients at least every three months. One of us also, the roentgenologist, has kept a cross-index of all cases, and note has been made of all cases entering the hospital with cavities and also those developing cavities after entrance. The above two factors have made our work comparatively easy.

It is a characteristic of United States Veterans Bureau tuberculosis hospitals that they have a large turnover. The U. S. V. B. hospital at Livermore is no exception. Although its capacity is 318 beds, it is not unusual to discharge from 20 to 35 patients per month and admit about the same number. On that account, we did not find as many cavity cases available for study as we had expected. We deemed it advisable not to accept a case for consideration unless the patient had been in the hospital a year. A shorter time than a year we deemed not a fair trial, although we found later that of the cases we studied 27 per cent closed the first six months. Although our percentage was brought down on this account, this was partly equalized by the fact that some advanced cases died less than a year after entrance and were not taken into consideration.

Our available cases were still further diminished owing to a number having been given pneumothorax and some having undergone thoracoplasty or phrenicectomy.

We finally found 120 cases suitable for study. Of these, twenty-seven had bilateral cavitation, so that a total of 147 cavities were observed.

The question may be asked, when do we say a cavity has healed. This

brings up another question of *how* cavities heal. If we examine cavities which are healing, at two or three months' intervals by serial roentgenograms, we find the annular shadows growing gradually smaller and the outline of the cavity or the wall often more indistinct. Finally, a linear density or a small area of fibrosis with radiating lines only remains, complete healing having occurred. Occasionally, cavities disappear very rapidly, and apparently all density disappears, leaving no trace that a cavity ever existed. Cavities appear to heal in the following manner: The caseous necrotic tissue separates and is expelled by way of a bronchus. Some portions may be absorbed. In time, the walls of the cavity develop granulation tissue and become fairly clean. Fibrous tissue, which has been developing in the walls and around the cavity, gradually contracts, so that when the walls of the cavity are brought together everything is favorable for healing. Some authorities even suggest that regeneration of lung parenchyma (6) occurs with formation of new alveoli.

We therefore say a cavity has healed when an annular shadow or diminished density can no longer be seen in the X-ray films and is replaced by a small density or scar. We again repeat that it may disappear, leaving nothing to indicate the previous existence of a cavity. Occasionally a cavity may become obscured by a dense area as large as or larger than the original cavity. In such cases, the cavity may be shut in by a fibrous capsule and not be healed. We have not included such cases in our list of healed cavities.

Some may question the reliability of roentgenology in diagnosing cavities and determining their disappearance in the lung. So much work has been done in comparing roentgenograms taken before, or even after death, with the postmortem findings at necropsy that there is no longer any doubt as to the great reliability of the X-ray.

We do not mean that the X-ray is infallible. It is true that occasionally certain causes for error may exist, such as lack of visibility of an occasional very thin-walled cavity after resolution and absorption have taken place, and sometimes due to the fact that the cavity wall has not formed. Postmortem evidence, however, shows that these errors are very rare.

All our cases showing healing of cavities have also shown corresponding evidence of healing by other associated clinical facts. As a rule, the sputum became negative and finally disappeared. The general well-being of the patients improved. Their cough disappeared. Their

weight increased. They did well on less rest. Comparative study of their roentgenograms showed continued clearing of the infiltrated areas and increased fibrosis. Almost invariably their lesions continued to retrogress and they proceeded onward toward an arrest.

Some writers have attempted to classify cavities. Pinner (1) in the same article quoted above classifies cavities as (1) small multiple cavities, (2) round or slightly oval cavities, and (3) irregular-shaped cavities with dense walls.

Baum, Mebel and Kane (6) tried to classify cavities based on Ranke's concept of three stages in pulmonary tuberculosis. These writers believe that we can judge very often by the type of cavity, as seen in the X-ray, whether it is likely to heal. It has seemed to us that the circular or oval cavities with only a moderately thick wall are most prone to heal. Also, cavities situated in the upper two-thirds of the lung are more apt to heal than those in the lower third. An investigation along these lines would be most interesting but we must leave it for future study. The purpose of this paper is only to demonstrate how frequently cavities heal. We have not attempted, therefore, a pathological-anatomical classification, but for analytical purposes have classified cavities, as to size and number only, as (1) small,—less than 2.5 cm. in diameter; (2) large,—diameter 2.5 cm. or more; and (3) multiple,—two or more cavities in one lung.

To better illustrate our findings and conclusions, we have prepared tables 1 to 6.

Table 1 is a most complete resume of our entire study and the remaining tables are all deductions from this first table. A careful study shows much of interest.

The classification in this table, of minimal, moderately advanced, and far advanced, is made for the purpose of showing the effect of the amount of pulmonary involvement on the fate of cavities. It is based on the amount of infiltration as stated in the classification of the American Sanatorium Association, leaving out the size of the cavity as a determining factor.

A minimal lesion is one in which the amount of involvement is not more than the equivalent of the area from the second rib and fourth dorsal spine to the apex on one side.

A moderately advanced lesion is one in which both lungs may be involved but in which the total involvement does not exceed the equivalent of one-third to the total volume of one lung according to the severity of the infiltration.

TABLE 1

Study of cavities

GENERAL CLASSIFICATION	HOSPITALIZATION	SIZE OF CAVITIES (1: Less than 2.5 cm. 2: Over 2.5 cm. 3: Multiple)				SMALLER				LARGER				DISAPPEARED														STATE OF LESION AT END OF OBSERVATION												DIED
														Size 1				Size 2				Size 3						Progressive			Retrogressive			Arrested						
		Size 1	Size 2	Size 3	TOTAL	Size 1	Size 2	Size 3	TOTAL	Size 1	Size 2	Size 3	TOTAL	6 months	12 months	18 months	24 months	6 months	12 months	18 months	24 months	6 months	12 months	18 months	24 months	TOTAL	Size 1	Size 2	Size 3	Size 1	Size 2	Size 3	Size 1	Size 2	Size 3				
Cavities of right lung — Minimal	Interrupted																																							
	Continuous		1		1		1		1																					1										
Cavities of right lung — Moderately advanced	Interrupted	1	1		2		1		1																		1			1										
	Continuous	9	14	2	25	3	2		5	3	2		5	1	2		1	3	5	1	1		1		1	16	3	3		7	10	2								2
Cavities of right lung — Far advanced	Interrupted		1		1					1			1															1											
	Continuous	5	2	9	16	2		2	4		2	6	8	1	1				1						1	4	1	2	5	4	1	2			1				
Total		15	19	11	45	5	4	2	11	4	4	6	14	2	3		1	3	6	1	1		1		2	20	5	6	5	11	13	4			1				2
Cavities of left lung — Minimal	Interrupted																																							
	Continuous		2		2													1	1							2					2								
Cavities of left lung — Moderately advanced	Interrupted																																							
	Continuous	4	13	3	20	2	2	2	6			1	1		1		1	5	3	2						12		1	1	4	12	2								1
Cavities of left lung — Far advanced	Interrupted	2	13	1	4	1	1	1	3	1		1	2														1	1		1	1	1							
	Continuous	10	4	8	22	4	3		7	5			5		1			1	1			1	2	3		9	5		1	5	3	7							4
Total		16	20	12	48	7	6	4	16	6		2	8		2		1	7	5	2		1	2	3		23	6	2	2	10	18	10								5

| | | |

A far-advanced lesion is one with a more extensive involvement than a moderately advanced lesion.

Table 2 shows the number of cases studied and the number of cavities studied, with the number which healed and the percentage in each case.

Table 3 shows that 56, or 38 per cent, of the cavities studied were small cavities; 44, or 30 per cent, were large cavities; and 47, or 32 per cent, were multiple cavities. It appears that each of these types of cavities is very evenly distributed in the right and left lungs.

Of small cavities, 37, or 66 per cent, healed and 10, or 18 per cent, became smaller, making a total of 47, or 84 per cent, either healing or becoming smaller.

Of large cavities, 10, or 23 per cent, healed and 20, or 45 per cent, became smaller, making a total of 30, or 70 per cent, either healing or becoming smaller.

TABLE 2

Number of cavities disappearing in relation to the number of cases

	NUMBER OF CAVITIES STUDIED	CAVITIES CLOSED	PERCENTAGE
Cases	120	48	40%
Cavities	147	62	42%

Of multiple cavities, 15, or 32 per cent, healed, and 10, or 21 per cent, became smaller, making a total of 25, or 53 per cent, either healing or becoming smaller.

Small cavities, 84 per cent, large cavities, 70 per cent, and multiple cavities, 53 per cent, either healed or became smaller. Taking all cavities into consideration, 69 per cent either healed or became smaller.

From the above, it is plain that the healing of cavities depends greatly on their size.

Some years ago it was customary to hear that a left-sided lesion had more difficulty in healing than a right-sided lesion on account of the heart's action not allowing the left lung to rest. In our series of cavities, leaving bilateral cavities out of consideration, 44 per cent of cavities healed in the right lung and 48 per cent in the left lung.

If we consider cavities which either healed or became smaller, we find that 69 per cent were cavities of the right lung and 83 per cent of the left lung. The left lung, therefore, appears to have some advantage over the right lung in the healing of cavities.

TABLE 3

Study of cavities in relation to size and location

	SMALL CAVITIES								LARGE CAVITIES								MULTIPLE CAVITIES								TOTAL	PER CENT
	Right lung		Left lung		Bilateral		Total	Per cent	Right lung		Left lung		Bilateral		Total	Per cent	Right lung		Left lung		Bilateral		Total	Per cent		
Number of cavities considered	19		20		17		56	38	15		16		13		44	30	11		12		24		47	32	147	
Became larger	4		0		5		9	16	4		6		4		14	32	6		2		14		22	47	45	31
		per cent		*per cent*		*per cent*				*per cent*		*per cent*		*per cent*				*per cent*		*per cent*		*per cent*				
Became smaller	4	21	6	30	0		10	18	5	33	7	44	8	61	20	45	2	18	4	33	4	16	10	21	40	27
Disappeared	11	58	14	70	12	70	37	66	6	40	3	19	1	8	10	23	3	27	6	50	6	25	15	32	62	42
Number of cavities which became smaller or disappeared	15	79	20	100	12	70	47	84	11	73	10	63	9	69	30	68	5	45	10	83	10	41	25	53	102	69

Table 4 shows that the healing of cavities depends not only on their size but also on the amount of pulmonary involvement.

Cavities heal, as stated above, by expulsion, absorption and contraction, bringing into contiguity granulating surfaces. If the lung is densely and extensively infiltrated, absorption becomes impossible, the cavity increases in size by further breaking-down of areas of caseation in the cavity walls, and contraction cannot take place.

TABLE 4

Disappearance of cavities in relation to the amount of involvement and location

CLASSIFICATION OF INVOLVEMENT	RIGHT LUNG			LEFT LUNG			BILATERAL			TOTAL STUDIED	TOTAL DISAPPEARED	PER CENT
	Number studied	Disappeared	Per cent	Number studied	Disappeared	Per cent	Number studied	Disappeared	Per cent			
Minimal.....	1	0	0%	2	2	100%	0	0	0%	3	2	66%
Moderately advanced.	27	16	60%	20	12	60%	8	6	75%	55	34	61%
Far advanced.....	17	4	24%	26	9	35%	46	13	28%	89	26	30%
Total.....	45	20	44%	48	23	48%	54	19	35%	147	62	42%

TABLE 5

Time of disappearance of cavities in relation to size

TIME OF DISAPPEARANCE	LARGE		SMALL		MULTIPLE		TOTAL	PER CENT
months								
6	2	20%	13	35%	2	14%	17	27%
12	5	50%	16	43%	5	33%	26	42%
18	0	0%	3	8%	3	20%	6	10%
24	3	30%	5	14%	5	33%	13	21%
	10		37		15		62	

According to table 4, 66 per cent of cavities heal in minimal cases, 61 per cent in moderately advanced, and only 30 per cent in far-advanced cases. Twice as many cavities heal when the involvement is in the minimal and moderately advanced classes as when it is in the far-advanced class.

Table 5 shows clearly the time of disappearance of cavities in relation to size.

Of the cavities which healed, 78 per cent of the small cavities, 70 per cent of the large cavities, and 47 per cent of the multiple cavities closed within twelve months. Taking the cavities as a whole, including all three types, 69 per cent healed within twelve months.

Going a little further, we find that 86 per cent of the small cavities, 70 per cent of the large cavities, and 67 per cent of the multiple cavities healed within eighteen months. Including all three types, 79 per cent healed within eighteen months.

The above data are very suggestive in deciding when to resort to pneumothorax or thoracoplasty. If cavities have not healed within eighteen months, the chances of healing later are very slim.

In deciding on our treatment for cavity cases, shall we depend on rest or shall we resort to pneumothorax or thoracoplasty?

TABLE 6

Rest treatment compared to pneumothorax and thoracoplasty in closing cavities

	NUMBER OF CAVITIES CLOSED	CAVITIES CLOSED	PERCENTAGE
Rest	147	62	42
Pneumothorax*	427	167†	39
Thoracoplasty*	36	13§	36

* Peters.

† Good collapse

§ Successful

Table 6 may help us in our decision. If we resort to rest, 42 per cent of the cavities will close. We will attain a good collapse in 39 per cent of the cases if we resort to pneumothorax.

Thoracoplasty will be successful in about 36 per cent. In coming to our decision, we must not forget that in our pneumothorax cases fluid will occur in about 70 per cent. Of these about 20 per cent will develop pus and a smaller 7 per cent will develop true empyema.

SUMMARY

Studied 120 cases: 48, or 40 per cent, healed.

Studied 147 cavities: 62, or 42 per cent, healed.

Small cavities, 56: 37, or 66 per cent, healed; 10, or 18 per cent, became smaller: 84 per cent either healed or became smaller.

Large cavities, 44: 10, or 23 per cent, healed; 20, or 45 per cent, became smaller: 68 per cent either healed or became smaller.

Multiple cavities, 47: 15, or 32 per cent, healed; 10 or 21 per cent, became smaller: 53 per cent either healed or became smaller.

Small cavities: 58 per cent in right lung and 70 per cent in left lung healed.

Large cavities: 40 per cent in right lung and 19 per cent in left lung healed.

Multiple cavities: 27 per cent in right lung and 50 per cent in left lung healed.

In cases classified minimal, 66 per cent of cavities healed.

In cases classified moderately advanced, 61 per cent of cavities healed.

In cases classified far advanced, 30 per cent of cavities healed.

Of small cavities that healed, 35 per cent healed in 6 months. 78 per cent in 12 months, and 86 per cent in 18 months.

Of large cavities that healed, 20 per cent healed in 6 months, 70 per cent in 12 months, and 70 per cent in 18 months.

Of multiple cavities that healed, 14 per cent healed in 6 months, 47 per cent in 12 months, and 67 per cent in 18 months.

Bilateral cavities, cases 54: 19, or 35 per cent, healed.

Bilateral cavities, cases 54: 5, or 9.3 per cent, healed, both lungs.

Hospitalization interrupted, 13 cases: cavities healed, 4, or 30 per cent.

Hospitalization uninterrupted, 107 cases: cavities healed, 44, or 41 per cent.

CONCLUSIONS

1. We found in our investigations that a surprisingly large percentage of cavities healed, rather than a small minority as stated by some writers.

2. We found that the ability of cavities to heal depended greatly upon two factors: (1) the size of the cavity, and (2) the amount of the pulmonary involvement.

3. The rest treatment appears to us of greater importance in the healing of cavities than artificial pneumothorax, thoracoplasty, or other surgical measures. In the average cavity case, which is not definitely retrogressive, and is without elevation of temperature, rest should be the treatment selected for at least twelve or eighteen months. Then if the cavity shows no tendency to heal, we should resort to pneumothorax or other surgical procedure in suitable cases.

4. In bilateral cavitation, the prognosis is not good. In only 9.3 per cent of these cases did the cavities heal in both lungs.

5. In order to attain the best results, rest must be prolonged, continuous, and without interruption. Patients with cavitation should rest from 20 to 24 hours daily. In our series, it was found that, when the patient's treatment was interrupted, 30 per cent of the cavities healed, while, when the hospitalization was continuous, 41 per cent healed.

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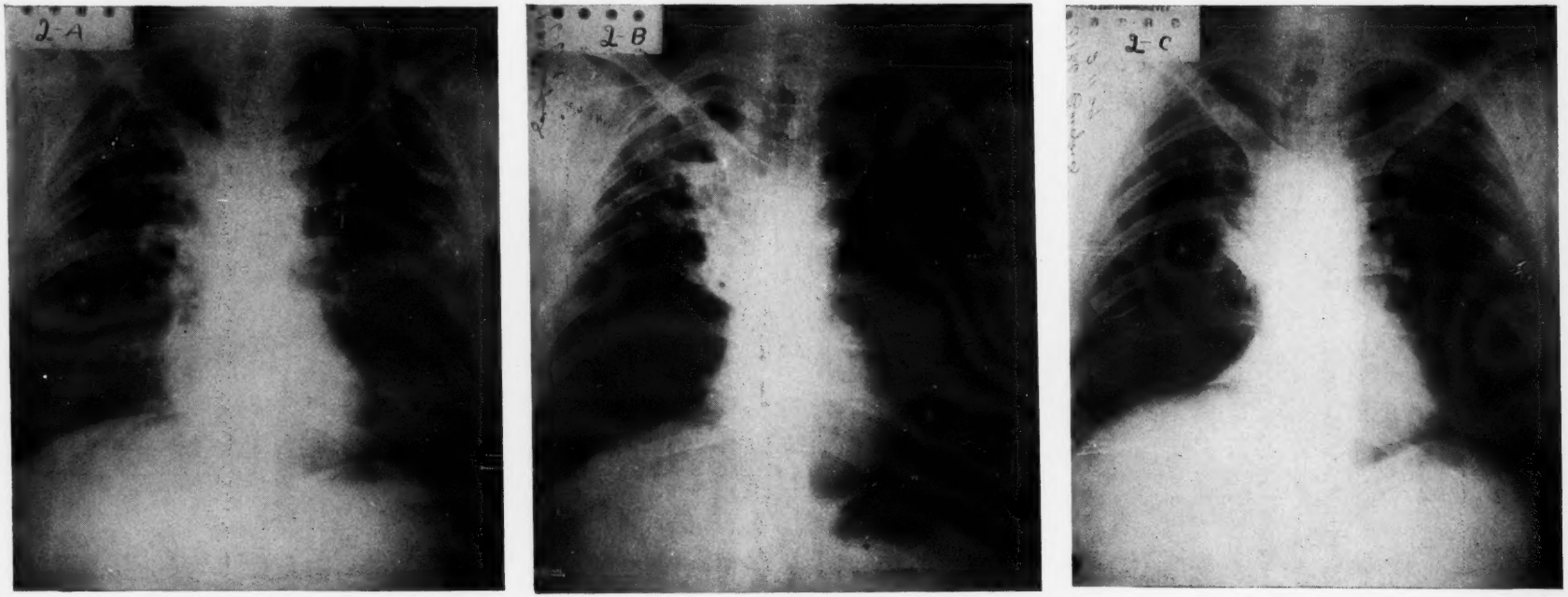


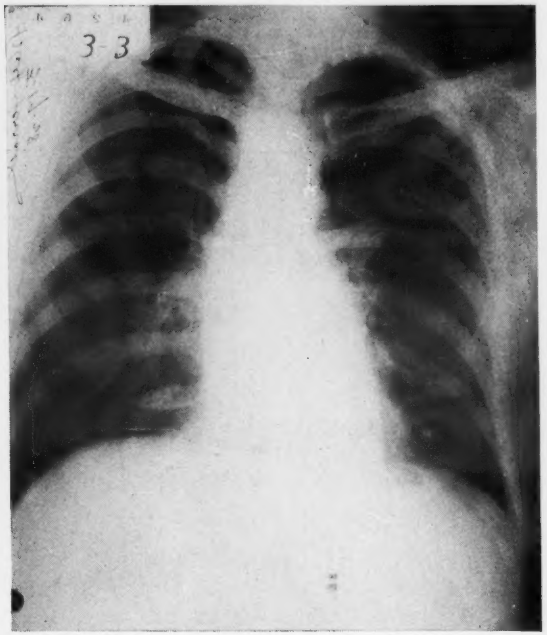
PLATE 1

Series 2

2A: Stereoroentgenograms taken June 1, 1927. Large cavity right upper lobe

2B: Stereoroentgenograms taken June 6, 1928. By comparison with films taken June 1, 1927, it is seen that the cavity has very much increased in size

2C: Stereoroentgenograms taken February 11, 1929. Comparison with films taken June 6, 1928, an interval of eight months, shows cavity to be healed



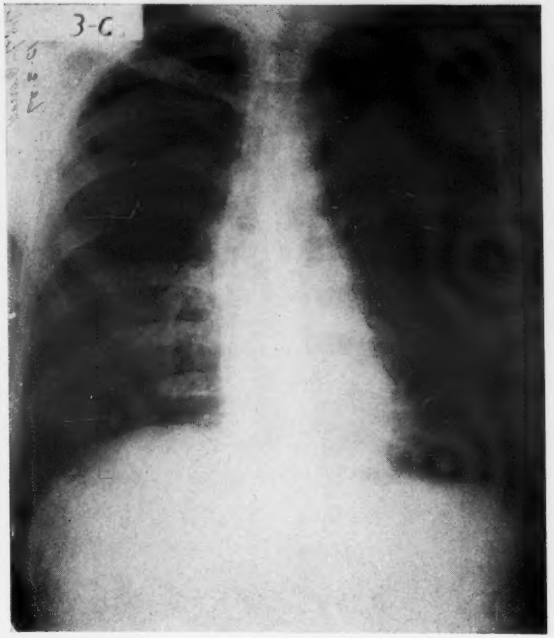


PLATE 2

Series 3

3A: Stereoroentgenograms taken September 21, 1927. Large cavity second interspace, left.

3B: Stereoroentgenograms taken March 19, 1928. Comparison with films taken September 21, 1927 shows cavity to have healed, a scar only remaining.

3C: Stereoroentgenograms taken December 3, 1929. Comparison with films taken March 19, 1928, shows that even the scar has disappeared, there being no evidence that cavity ever existed.

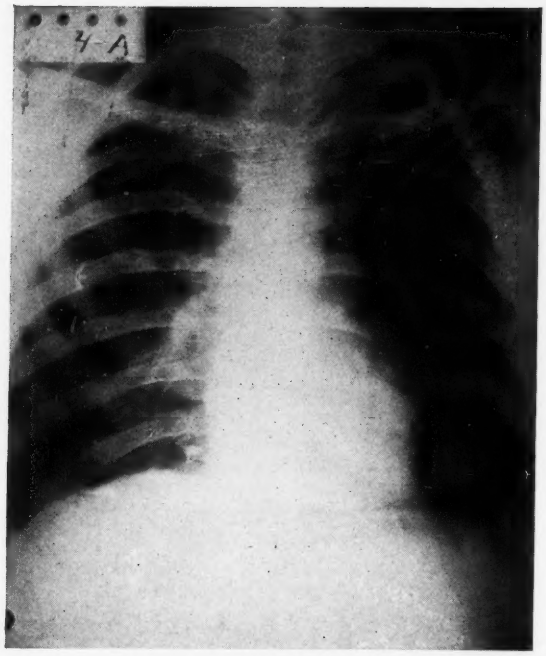


PLATE 3

Series 4

4A: Stereoroentgenograms taken May 22, 1928. Large cavity may be seen at apex, left lung.

4C: Stereoroentgenograms taken February 18, 1929. Comparison with films taken May 22, 1928, shows cavity to have healed, only a slight scar remaining.

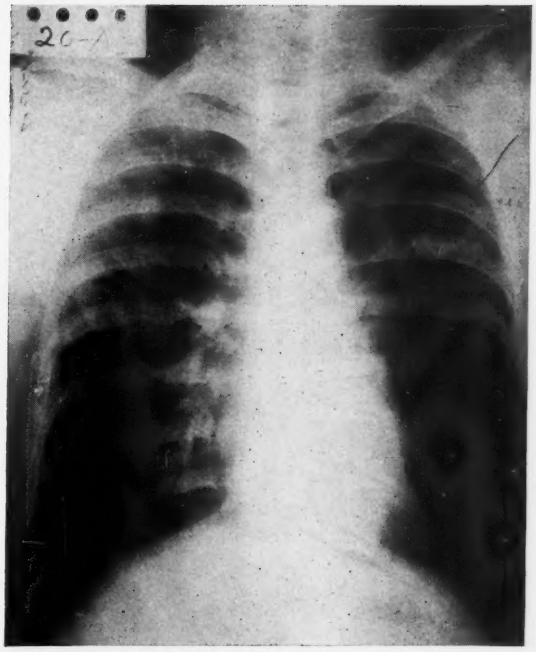


PLATE 4

Series 20

20A: Stereoroentgenograms taken January 15, 1929. Large cavity, left lung.

20B: Stereoroentgenograms taken October 18, 1929. Comparison with roentgenograms taken January 15, 1929 shows cavity to have healed, a scar only remaining.

OBSERVATIONS ON THE EFFECTS OF SMALLPOX VACCINATION ON TUBERCULOSIS PATIENTS[1]

REUBEN E. STONE[2]

During the past year, because of the more or less widespread prevalence of smallpox throughout the country, it became necessary to vaccinate all of the patients at Koch Hospital who had not been successfully vaccinated recently. The vaccination of such a large number of patients offered us an opportunity to make observations on the clinical reactions in a fairly large group of tuberculosis patients and from this study to determine whether such an added prophylactic measure is or is not contraindicated in tuberculosis.

The work done by other observers is apparently very meagre as a perusal of literature reveals only a few papers on the subject. Fishberg (1) states that, although he himself has had no experience with smallpox, he nevertheless sees no apparent contraindications to vaccination in view of the fact that the mortality from tuberculosis has declined in all the civilized countries in which vaccination has been general.

Koch Hospital has approximately 500 patients, both white and colored, men, women, and children. Of this number, 337 were vaccinated and there were 104 positive reactions or 30 per cent. The following table gives number and percentages according to groups and reactions:

	vaccinated	*takes*	*per cent*
White females	125	27	21.6
Colored females	18	5	21.7
White males	164	57	34.1
Colored males	17	7	41.2
White children	3	3	100.0
Colored children	10	5	50.0

All stages and types of pulmonary tuberculosis were represented in this composite of patients. The largest percentage of the patients vaccinated fall under the classification of the far-advanced class-I group, and they graduate down to a comparatively small percentage of the incipient class-V group. While each patient is individually considered, the follow-

[1] Read before the Trudeau Club, St. Louis, Missouri, June 5, 1930.

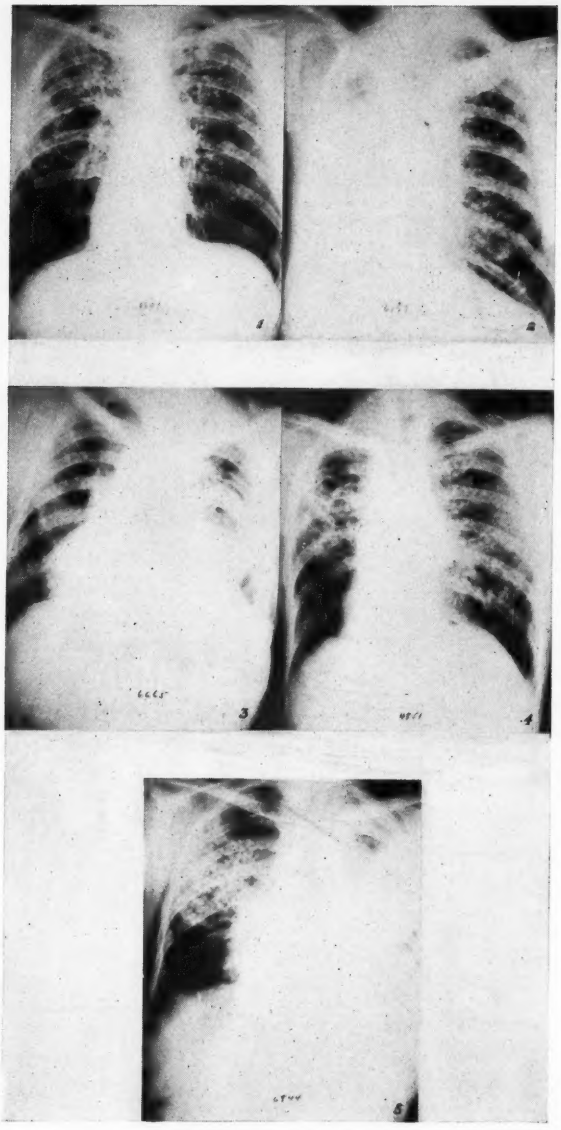
[2] Robert Koch Hospital, St. Louis, Missouri.

ing rules, although there are exceptions, give a fair idea of what is meant by classes I to V:

Class I: Includes patients with a temperature of 100°F. or over and strictly bed-patients.
Class II: Patients running a temperature of 98.8°F.; are bed-patients, but are given toilet privileges.
Class III: Patients running normal temperatures; are up between the following specified rest periods: 8 to 9:30 A. M.; 10 to 11:30 A. M.; 1 to 3:00 P. M.; 3:30 to 4:30 P. M.
Class IV: Patients showing a normal temperature; have their clothes; may sit on settees on the grounds, but have no exercise assigned.
Class V: Patients showing a normal temperature; are assigned to certain specified forms of exercise.

In order to arrive at a just conclusion, the various results noted in such diversified classes of patients must be weighed rather carefully, and in the interpretation of the apparently unfavorable reactions one must take into consideration the patients' clinical condition and the extent of the pulmonary involvement at the time of vaccination.

Observations were made on fever, pains, cough, expectoration, X-ray and physical findings of the chest. All the patients showed a rise in temperature of from one to three degrees F. For a period of a week or ten days most of the patients had the general symptoms of a secondary infection. In many of the patients the healing of the wound was prolonged, the scabs were larger, the underlying ulcers deeper and more painful, and the areas of circumscribed erythema larger than one would expect in normal individuals. The far-advanced, class-I group showed the most discomfort, due to above-mentioned evidence of a positive reaction. One class-II patient who was vaccinated for the first time was made worse temporarily. She was vaccinated upon the thigh and eight days later she had a rise in temperature of two degrees. Subsequently, a scab developed, about one and one-half inches in diameter, and an area of erythema, about six inches in diameter, was noted. Râles were heard in the base of the left lung. An X-ray showed only a questionable increase in the lung markings on that side. A chronic idiopathic salpingitis was exacerbated. Four months after the vaccination the patient was still in class I, and the erythema was still present. The local pain and tenderness and the râles in the base of the lungs had disappeared. Five months after the vaccination her tuberculous condition



Interpretation of Figures 1 to 5

The X-ray pictures which were taken before the vaccination show the large amount of pathological involvement present in five of the patients who died, and it is evident from these plates that these patients had no chance for recovery had they not been vaccinated, and it is my opinion that in no case was the vaccination in any way responsible for the outcome.

FIG. 1. Plate 6801 shows very heavy fibrotic changes throughout the entirety of each lung, with areas of consolidation and cavity-formation in each upper lobe.

FIG. 2. Plate 6123 shows a consolidation in the left lung with a large cavity in the upper lobe. The right lung shows heavy fibrotic changes throughout with definite evidence of activity below the clavicle.

FIG. 3. Plate 6665 shows a heavy infiltration in the right lung with a small area of pneumothorax and cavity-formation in the upper half. The markings in the left lung show evidence of activity.

FIG. 4. Plate 4851 shows extensive involvement of the upper half of the left lung with large cavity-formation. The right lung shows marked involvement throughout.

FIG. 5. Plate 6844 shows a consolidation throughout the right lung and middle third of the left lung, with cavity-formation in the left apex.

had improved markedly, and later her condition became better than it had been at any time since her admission to the hospital. The question raised was whether the reaction caused the subsequent improvement. Two patients claimed that their cough was aggravated and that the amount of sputum was slightly increased. However, these manifestations lasted only for a few days, following which they subsided. To date, 7 patients of the number who were vaccinated have died. One died of tuberculous meningitis, one of a markedly active Pott's disease with multiple sinuses in the lumbar region, and the other five because of their extensive pulmonary involvement. The X-ray pictures appended show the large amount of pathological involvement present in each case, and I am of the opinion that death in none of these cases was precipitated by the vaccination. None of the patients, with the exception of those mentioned above, showed any clinical signs or X-ray findings of a pulmonary aggravation nor did they manifest increased tuberculous intoxication.

To recapitulate, only one patient showed any definite pulmonary exacerbation, and two patients showed a temporary increase in one or two symptoms (cough and expectoration). The remainder of the patients showed no changes following vaccination. In other words, three patients out of a total of 337, or nine-tenths of one per cent who were vaccinated, showed some tuberculous changes. If we consider the usual mortality in a smallpox epidemic and the probable increase in mortality in a group of persons already weakened by disease, then the very few unfavorable results noted should not be set up as a contraindication to vaccination. On the contrary, vaccination should be recommended in tuberculosis, either active or nonactive, as a justifiable prophylactic measure.

It is interesting to note that this conclusion compares favorably with the conclusions reached by some workers who have observed the results of typhoid vaccination in tuberculosis. Bald and L'Esperance (2) found that animals were apparently unharmed by typhoid vaccine. Russel and Nichols (3) claim that "in the presence of a typhoid epidemic, tuberculosis, either active or latent, is not a contraindication to typhoid vaccination."

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(2) Jour. Immunol., 1916, ii, 283.
(3) Jour. Amer. Med. Assoc., 1921, lxxvi, 177.

THE EFFECT OF QUININE ON THE TUBERCLE BACILLUS[1]

ABRAHAM J. LEVY

The derivatives of cinchona have been in use for centuries for antipyresis. Therapy with this drug was more empirical than rational, because the *modus operandi* of the active principle of the alkaloid was unknown. As early as 1868 Binz (1) suggested that quinine renders the malarial toxin inert. But not until after the discovery of the malarial plasmodium by Laveran in 1880 did the actual effect of quinine begin to attract the attention of investigators. Binz experimented on the amoeba, on various types of infusoria and on leucocytes. In each case he found that the protoplasmic rather than the nucleic portion of the cell underwent regressive changes. Hence quinine was termed a "protoplasmic poison." Binz also found that when this drug was allowed to act on the protozoa or infusoria in minute quantities, it increased their motility. When used in large amounts, however, these organisms were instantly paralyzed. The infusoria were killed in large number in dilutions of 1:6,000 to 1:20,000. Malarial organisms were killed by a concentration of 1:5,000.

Many other investigators (2) (3) studied the effect of quinine on various types of bacteria. The growth of typhoid bacilli was found to be inhibited in dilutions of 1:30,000, but these organisms were not killed by dilutions as low as 1:100. The effect of quinine on anthrax, diphtheria and tetanus bacilli, pneumococci, staphylococci and streptococci have also been reported (4) (5). For some time quinine was fostered by some workers as the only remedy for pneumonia (6) (7) (8) (9). Ethylhydrocuprin, a derivative of quinine, was, for a time, hailed as a specific therapy for pneumonia (10), but the great toxicity (11) (5) of the drug was responsible for the fact that quinine was discarded as a therapeutic agent in pneumonia.

Only a few reports about quinine therapy in tuberculosis have been found in the literature (12) (13) (14), but up to date no investigator has made a special study of the effect of quinine on tubercle bacilli both *in vitro* and *in vivo*. In the present investigation the problem at first con-

[1] From the Research Laboratories of the City of Chicago Municipal Tuberculosis Sanitarium.

sisted of the collection of scientific data dealing with the direct action of this drug upon the acid-fast organisms rather than with the application of the drug for therapeutic use.

The problem—the effect of quinine on tubercle bacilli—has been taken up, because, so far, there seems to have been no mention made on this subject in the literature of the past half-century.

The effect of quinine on tubercle bacilli was considered and studied from two angles, namely, *in vitro* and *in vivo*. This paper will deal first with a discussion of the experiments performed.

IN VITRO

Experiment 1

Object: To study the effect of quinine on the growth of the tubercle bacilli when the drug is mixed in the culture medium.

Procedure: Quinine hydrochloride was used throughout the experiment because it is highly soluble in water (1:1).

Ten grams of quinine hydrochloride were dissolved in 100 cc. of the glycerin-agar medium used at the Municipal Tuberculosis Sanitarium (Chicago). From this basic solution the following dilutions were made: 1:10; 1:100; 1:1,000; 1:10,000; 1:50,000 and 1:100,000.

The medium was sterilized, tubed and allowed to cool in slants. The tubes were incubated for 96 hours, in order to check on the sterility of the medium. These slants were used for inoculation.

Tubercle bacilli, human strain, 175A, were used in this experiment. A heavy suspension of tubercle bacilli was prepared by macerating a good growth with 2 cc. of normal salt solution. Five tubes of each dilution of the cinchonized medium were inoculated with this heavy suspension of tubercle bacilli. As a control five tubes of plain glycerin-agar medium were also streaked with the same emulsion.

After two weeks, readings were made weekly to determine the presence and rate of growth. At the end of five weeks a very scanty growth appeared on four of the tubes on 1:100,000 dilution and on all the control tubes. Three months after inoculation a luxuriant growth was found in the tubes of dilution 1:100,000 and in the control, but no growth was present in any of the tubes of the other dilutions[2] (figure 1).

[2] A whitish precipitate was formed on the surface of the slants in quinine dilutions of 1:10 and 1:100. This precipitate was limited to the area of inoculation, and it is probably due to some unknown physiochemical reaction between tubercle bacilli and quinine in low dilution. No growth was shown in these tubes at any time during the 6 months of experimentation.

Smears prepared from tubes of all dilutions and from the controls were stained with the usual carbol-fuchsin stain method used at the Sanitarium. The smears made from tubes of 1:10 up to 1:50,000 dilution showed no normal organisms, but contained pin-point bits of acid-fast material in streptococcic arrangement (figures 2 and 3). All these tubercle bacilli apparently were in a stage of disintegration and were of equal degree in all tubes mentioned above.

Smears from tubes of 1:100,000 dilution and from control tubes showed normal tubercle bacilli (figures 4 and 5).

Conclusions: The growth of the tubercle bacilli was not only inhibited, but the organisms planted on the slant also underwent degeneration in the usual glycerin-agar medium into which quinine in dilution of from 1:10 to 1:50,000 was present. On the other hand, the organisms in the tubes containing quinine in dilution of 1:100,000 grew luxuriantly, similar to that of the control.

Experiment 2

Object: To study the effect of time-exposure of the tubercle bacilli to various dilutions of quinine ranging from 1:10 to 1:100,000.

Procedure: Dilutions of quinine solution 1:10 to 1:100,000 in distilled water were prepared and then sterilized in the Arnold sterilizer. After the solutions were cooled, 0.5 cc. of a heavy suspension of tubercle bacilli, strain 175A, was added to 5 cc. of each dilution of quinine. For control, 0.5 cc. of the suspension of organisms was added to 5 cc. of distilled water. Then the tubes were placed in the incubator for 30 minutes. When they were removed from the incubator the suspension of organisms in the first three tubes (1:10, 1:100, 1:500) seemed to settle at the bottom. In the first tube there was a marked degree of clumping, similar to agglutination in the macroscopic Widal test. The degree of clumping varied with the degree of concentration of the quinine solution; that is, the higher the concentration, the coarser the clumping. In the control and in the dilutions of 1:1,000 and up to 1:100,000 the homogeneous suspension persisted as before incubation. At this point the experiment was divided into two parts. In the first part the series of tubes were inoculated with organisms which were incubated in quinine solution only from 30 to 40 minutes. In the second part of the experiment, on the other hand, the tubes containing the media were inoculated with tubercle bacilli, which were incubated in the various quinine dilutions from 120 to 130 minutes. At first glycerin-agar medium was used for inoculation,

but, when after four weeks there was no sign of growth[3], the modified Petroff medium (15) developed in this laboratory was substituted. This medium is very sensitive and had given about 99 per cent of good results in growing this type of organism. Tubes containing modified Petroff's medium were inoculated with two loopfuls of organisms from various dilutions of quinine as prepared above. In order to check on the results, five tubes from each dilution were inoculated.

Since this medium is very sensitive to the growth of the tubercle bacilli, the tubes thus inoculated were watched for the first signs of growth.

TABLE 1

SERIES	DILUTIONS	GROWTH			REMARKS
		7 days	*10 days*	*15 days*	
I After 30 minutes' incubation	1:10	0	0	+	
	1:100	0	0	+	
	1:500	0	0	++	
	1:1000	0	+	+++	
	1:5000	+	++	+++	
	1:10000	++	+++	++++	
	1:50000	++	+++	++++	
	1:100000	++	++++	++++	
	Control	+++	++++	++++	
II After 120 minutes' incubation	1:10	0	0	0	
	1:100	0	0	0	
	1:500	0	0	0	
	1:1000	0	0	+	
	1:5000	0	+	++	
	1:10000	0	+	++	
	1:50000	++	+++	+++	
	1:100000	−−	−−−−	−−−−	Contamination
	Control	++	++++	++++	No growth

Tubes inoculated on May 30, 1929, showed the first signs of growth seven days later, as shown in table 1.

Summary: It is seen that a 1:500 solution of quinine is bactericidal to tubercle bacilli at 120 minutes' exposure, but it is only bacteriostatic at 30 minutes' exposure

Conclusion: The above experiment demonstrates that quinine has a definitely deleterious effect on the tubercle bacilli, varying directly with the period of exposure, and the concentration of the drug. It having

[3] Even 5 months later there was no sign of growth on the glycerin-agar.

been demonstrated that quinine is toxic to the bacillus *in vitro*, experiments were devised to determine whether this toxicity also existed in *in vivo* experiments.

IN VIVO

Experiment 1

Object: To study the reaction of animals to the injection of tubercle bacilli which have been exposed to quinine solutions of various concentrations for varying periods.

Procedure: Twelve guinea pigs were selected for this experiment. These guinea pigs were young and healthy and were fed a good diet prescribed by Miss Grant. In series 1, five guinea pigs were inoculated with tubercle bacilli which had been incubated for 30 minutes with various concentrations of quinine solutions similar to those prepared in the previous experiment[4].

Series I

guinea pig	*quinine solution*
1	1:10
2	1:100
3	1:1000
4	1:10000
5	1:100000
11	Control, no quinine

The organisms for the control were incubated in diluted saline solution for the same period of time as the organisms in the cinchonized solution. One guinea pig was used for control for each series.

In the second group (series II) 5 guinea pigs were inoculated with the same organisms and the same dilution of quinine solution, except that the time of incubation was increased to 120 minutes.

Series 2

guinea pig	*quinine solution*
6	1:10
7	1:100
8	1:1000
9	1:10000
10	1:100000
12	Control, no quinine

All the animals were inoculated subcutaneously in the abdominal wall with 0.5 cc. of the respective suspension of organisms. As indicated

[4] Here also the phenomenon of clumping was observed, as described in experiment 2 *in vitro*.

above, the guinea pigs were weighed before inoculation, the weight varying between 200 and 225 gm.

The following observations were made: Five minutes after guinea pig 1 was injected with tubercle bacilli in a 1:10 quinine solution, it was found to be in anaphylactic shock. Its hair was ruffled, it was unable to maintain its equilibrium, and it finally lay on its side with front and hind legs very flaccid. Respiration was deep and rapid. The animal remained in a comatose condition for about 12 hours, but gradually recovered and was in good condition in 24 hours from the time of inoculation.

Animal 6 was inoculated with the same suspension of organisms, but the period of incubation of suspension was longer, that is, 120 minutes. This animal did not undergo the same kind of shock as animal 1, but was found dead the next morning. Autopsy showed some inflammatory reaction of the subcutaneous tissue at the site of inoculation. No other pathological change was visible.

It seems that when the tubercle bacilli were incubated in quinine solution of 1:10 concentration, a toxic substance was formed or liberated by these organisms which was very fatal to the guinea pigs. In order to rule out the effect of quinine alone of the same concentration on the guinea pigs, three other animals were injected with 0.5 cc. of quinine solution 1:10. The animals showed no reactions and lived a long time. All the other guinea pigs showed no reactions to the injections.

In order to study the rate of growth of the animals, they were weighed once a week. All animals were kept on the same diet. Results are found in table 2.

All the animals lived four months except nos. 3 and 6. These died in the early part of the experiment and animal 9 died about a week before the end of the experiment.

The gain in weight of the animals indicates that the tuberculous infection was not rapidly progressive, since tuberculosis is usually accompanied with a loss of weight. The first animal of the first series (1) and the second and third in the second series (nos. 7 and 8) weighed over 550 gm. for some time during the experiment. All the other animals weighed about 500 gm., some slightly above, others slightly below. The control animals never reached the weight of 450 gm. (no. 11 reached 425 gm. while no. 12 reached 435 gm., the highest point). About the end of the second month the inguinal lymph nodes of all the animals except nos. 1, 7 and 8 were palpable. At the end of the experiment the inguinal lymph nodes of all the animals without exception were enlarged.

At the end of the fourth month, the animals were chloroformed and autopsied, and the lungs, liver, spleen and lymph nodes were examined for tuberculosis. The following is a summary of the pathological changes found on autopsy.

Series I: Lungs: The lungs of all animals showed some tuberculous process, except for guinea pig 1, which showed no involvement. The tubercles in the lungs of guinea pigs 2 and 3 were distinguished from those

TABLE 2

Body weight of guinea pigs in quinine experiment

GUINEA PIGS	DATES AND WEIGHTS IN GRAMS																REMARKS
	Initial 5-23	6-6-29	6-15-29	6-22-29	6-29-29	7-5-29	7-12-29	7-19-29	7-26-29	8-2-29	8-9-29	8-16-29	8-23-29	8-29-29	9-9-29	Final 9-20-29	
Series I																	
1	215	318	384	417	395	437	466	483	494	518	537	555	566	575	570	585	
2	210	312	355	377	380	401	425	422	438	452	456	457	473	478	491	482	
3	202	300	320	297	287	275	247	Died									Died 7–13–29 and weighed 230 gm.
4	200	298	307	327	342	368	383	397	404	458	480	485	501	492	455	430	
5	220	350	362	392	390	421	427	437	448	461	488	492	486	503	453	445	
Control																	
11	212	335	368	380	362	387	367	406	425	400	398	393	373	365	357	340	
Series II																	
6	206	Died															Died 5–24–29
7	218	330	400	447	442	501	513	557	578	575	607	622	633	623	590	582	
8	210	325	390	392	390	450	475	485	520	514	530	517	553	560	555	590	
9	202	325	370	395	382	425	432	430	442	440	428	413	400	357	Died		Died 9–4–29
10	225	360	368	385	378	420	456	457	488	487	498	504	482	507	505	515	
Control																	
12	204	210	275	308	306	356	385	390	413	398	388	415	430	435	408	390	

of guinea pigs 4 and 5 and the control, in that the former contained numerous pin-point tubercles, while the others were full of large tubercles, mostly caseous.

Spleen: The spleen of guinea pig 1 was about normal and contained two tubercles. On the other hand, the spleen in the other animals, including the control, was enlarged. The enlargement varied from about two to eight times normal size. All, including the control, were riddled with miliary tubercles.

Liver: The liver of all the animals was somewhat enlarged except that of animal 1. Only the liver of guinea pigs 3 and 4 and the control demonstrated gross lesions of tuberculosis of either pin-point or patches type, while others were free from macroscopic lesions.

Lymph Nodes: The inguinal lymph nodes of all the animals were enlarged bilaterally. A large number of them were caseous.

Kidneys: Only the kidneys of guinea pig 3 which died on July 13 and the control showed evidence of tuberculosis. The others were negative.

Testicles: The testicles of both guinea pig 3 and the control were atrophied bilaterally, while those of guinea pig 4 contained a large caseating cavity on the left.

Sections for microscopic studies were made only when the gross appearance of the tissue was suspicious of tuberculous lesions. All sections examined showed patches of passive hyperaemia, small round-cell infiltrations and a number of areas with epithelioid cells. No giant cells were detected in any section except in the spleen of the control animal.

Series II: Lungs: Numerous pin-point tubercles were noted in the lungs of guinea pigs 9 and 10, and in the control of this group. The lungs of guinea pigs 7 and 8 contained suspicious areas of consolidation. No specific tuberculous lesions were found in microscopic sections from these areas.

Spleen: As in series I, here also the spleen was unusually enlarged. The degree of enlargement in this series, however, surpassed that of the first series. The enlargements varied from about two to twenty-five times the normal size. The spleens of guinea pig 9 and the control (no. 12) were the largest,—twenty-five and fifteen times the normal size, respectively. With the exception of the spleen of no. 7, which contained one large cavity of tuberculous origin, all the others had numerous pin-point tubercles. Microscopic section disclosed the usual pathological involvement.

Liver: The livers of animals 9 and 10 and the control were enlarged and riddled with miliary tubercles. The livers of animals 7 and 8 were normal in size and negative for tuberculosis. Microscopic examination disclosed the usual pathological findings.

Lymph Nodes: The inguinal lymph nodes of all animals were enlarged and caseous.

Kidneys and Testicles: The kidneys and testicles were negative in this series.

Experiment 2

Object: To study the reaction of guinea pigs to tubercle bacilli, as modified by quinine treatment, which started three weeks after inoculation.

Procedure: A thick suspension of tubercle bacilli in saline solution was prepared and 0.3 cc. of the suspension was injected subcutaneously into the abdominal region of each of three guinea pigs, nos. 13, 14 and 15, which formed the third series of this experiment. These guinea pigs were watched carefully because they were injected with a heavy dose of tubercle bacilli. A week after inoculation they developed an area of induration at the site of injection. This induration was elevated and varied in size in different guinea pigs, ranging from 1 to 3 cm. in diameter. The mass just described was seemingly tender to touch. There was no discoloration or sloughing. Not until the end of the fourth week following the sloughing of the skin did these masses break out, revealing their cheesy contents. Inguinal lymph nodes were not palpable until the third and fourth weeks.

Three weeks after inoculation, the animals were each given 1 cc. of quinine suspension orally in olive oil. The quinine suspension was made by mixing 10 gm. of quinine in 100 cc. of olive oil. This oily suspension was preferred because the water solution interfered with digestion and affected the stomach wall of the animal (*cf.* below the autopsy on guinea pig 17). This treatment was repeated at first three times weekly and, after two months, six times weekly. In the sixth week the ulcers described above became quite deep and cheesy. These ulcers were anointed with an oil suspension of quinine. Gradually after eleven weeks these ulcers healed, leaving no scar.

Animal 13 died a short time after the beginning of the experiment. Autopsy disclosed a spleen about eight times larger than normal, dark red and mottled white. The liver was caseous; the lungs had tubercles in every lobe; the kidneys were shriveled badly; the stomach was a mass of ulcers at the fundus which almost broke through the wall. The mucosa showed a mass of haemorrhages. The diagnosis was generalized tuberculosis.

Animal 14 lived a short time and died about the seventh week. Autopsy disclosed liver and spleen normal in size and free from tuberculous lesions. All lobes of the lungs were filled with small tubercles. The diagnosis was tuberculosis of the lung. Inguinal lymph nodes were enlarged but not caseous.

Animal 15 lived longer than the former animals, until the end of the experiment, and finally was chloroformed. Three months and two weeks after the beginning of the experiment the animal developed paralysis of its hind limbs. Its body weight began to decline rapidly, although it continued to eat. (This paralysis developed in the laboratory in some animals which were not treated with quinine.) The autopsy revealed that the lymph nodes were slightly enlarged, but not caseous. The spleen and liver were normal in size and presented no tuberculous lesions. The lungs showed pin points of consolidation. The kidneys were badly shriveled.

Table 3 gives the body weight of these animals.

TABLE 3

Body weight of guinea pigs in quinine experiment

NUMBER OF GUINEA PIGS	DATES IN WEEKS AND BODY WEIGHT IN GRAMS																
	Initial 5-23	6-6-29	6-15	6-22	6-29	7-5-29	7-12	7-19	7-26	8-2-29	8-9	8-16	8-23	8-29	9-9	9-20	
Series III																	
13	220	310	318	317	288	288	245	Died									7–11–29
14	218	250	283	296	302	Died											7–1–29 weight, 297 gm.
15	214	250	261	269	282	302	338	333	363	370	375	366	357	342	390	210	

Discussion: Though the animals were inoculated with a massive dose of tubercle bacilli, nevertheless one of this group lived until the end of the experiment and showed very little active pathological change in comparison with the massive infection that was imparted to them. Whether the result of the survival of the guinea pig was due to quinine treatment one cannot say for certain, since the other pigs died. The guinea pigs gained weight very slowly and poorly. This experiment should be repeated in a larger number of animals to ensure satisfactory results.

Experiment 3

Object: To study the effect of quinine as a protective means against tuberculosis.

Procedure: Three guinea pigs, 16, 17 and 18, were chosen for this part of the problem. The animals were weighed (table 4) and each was given 0.5 cc. of quinine solution subcutaneously. This dose was repeated

three times a week The animals did not show any reaction to quinine solution 1:10 as did guinea pigs 1 and 6 in the first experiment. It is true that in some of these animals there was a sloughing of the skin at the site of the injection of the quinine, but the ulcers formed healed easily in a short time, leaving no scars.

At the end of the second week the animals were treated with 0.5 cc. quinine solution 1:10 by mouth instead of subcutaneous injections. This change was made in order to avoid further sloughing of the skin. Later it was found that even this method of quinine administration was not successful, for, it seems, the drug affected the digestive system of the guinea pigs. This was noted by the autopsy performed on guinea pig 17 which died at the end of the second week. A new method was then devised for administering the quinine. Ten grams of quinine were sus-

TABLE 4

Body weight of guinea pigs in quinine experiment

NUMBER OF GUINEA PIGS	DATES IN WEEKS AND BODY WEIGHT IN GRAMS															
	Initial 5-23	6-6-29	6-15	6-22	6-29	7-5-29	7-12	7-19	7-26	8-2-29	8-9	8-16	8-23	8-29	9-9	9-20
Series IV																
16	202	260	348	380	402	415	430	445	469	480	480	496	498	508	490	395
17	204															
18	210	290	359	367	370	404	438	448	484	493	510	522	512	528	525	565

pended in 100 cc. of olive oil and the guinea pigs were given first 0.5 cc. and later 1 cc. of this suspension by mouth three times weekly.

These animals were kept under the influence of quinine for three weeks previous to inoculation with tubercle bacilli. The purpose of this method of treatment was to create some protective power in the animals against the development of tuberculosis due to a massive infection. At the end of the third week after the beginning of the quinine treatment the animals were inoculated with 0.5 cc. of a thick suspension of tubercle bacilli, human strain 175A, in physiological salt solution.

After inoculation with tubercle bacilli the dose of quinine was increased first to four times and later to five times a week. The animals were gaining in weight gradually and showed no symptoms of illness.

At the end of the second week guinea pig 17 died and the autopsy performed on this animal disclosed no pathological change except for extreme

friability of the wall of the stomach and minute ulcerations which were surrounded by hyperaemic zones. This involvement was attributed to the effect of the quinine in water solution 1:10, and therefore an oily suspension was used later instead of the watery solution.

Table 4 gives the weekly progress of the body weight of the animals. Both animals were gaining in weight considerably, and, besides, at the end of three months showed no signs of enlargement of the inguinal lymph nodes. Moreover, these animals did not develop masses at the site of inoculation as those observed in animals 13, 14 and 15. Guinea pig 16 was reinoculated with a 0.3-cc. dose of tubercle bacilli as before, while animal 18 was not inoculated. This was done in order to observe the difference in reaction between both of these animals. Guinea pig 16 developed a swelling in the abdomen at the place of inoculation. The swelling was at first indurated and later became soft and threatened to rupture, but it subsided without ulceration. The animal became very ill, stopped eating for a while and the weight became stationary, but it gradually recovered and began to gain weight.

About two weeks before the end of the experiment the weight of animal 16 began to decline very rapidly (see table 4). Animal 18 was, on the other hand, gaining in weight up to the last days, when both animals were chloroformed, four months after the beginning of the experiment.

On autopsy, guinea pig 16 presented some caseation of inguinal lymph nodes, both right and left. The spleen was enormously enlarged,—about fifteen times the normal size,—and was dark red. The liver was enlarged and brownish. It appeared as if at some time during the experiment the animal had had tuberculous lesions. The heart muscle was whitish. The right, middle and upper lobes of the lungs presented caseous areas and some inflammatory condition. The right lower lobe contained several jelly-like tubercles which seemed to be shrunken.

Autopsy of animal 18 showed no enlargement of the inguinal lymph nodes on either side. The spleen was about twice normal size, with one suspicious spot of tuberculosis. All lobes of the lungs were filled with white tubercles surrounded by fibrous tissue. All the other organs were normal.

Discussion: Because of the limited number of guinea pigs that was allowed for this part of the experiment, one can hardly draw definite conclusions from the results. Nevertheless, it is rather suggestive that quinine may possess some prophylactic value against tuberculosis. This statement is based on the results demonstrated by guinea pig 18, which,

although inoculated with a heavy dose of tubercle bacilli, continued to gain constantly. Guinea pig 16 would probably have given the same pathological findings as guinea pig 18, were it not for the reinoculation. Although these results are not conclusive, they are suggestive and should be checked on a larger scale

GENERAL DISCUSSION

The experiments *in vitro* prove that there was a definite effect of quinine on the tubercle bacilli. When the organisms were cultivated on a cinchonized medium of various dilutions they underwent regressive changes in dilutions from 1:10 to 1:50,000, but they gave a luxuriant growth on a dilution of 1:100,000 even better than the control. This confirms the results of Binz (1) in his work on protozoa; namely, that quinine in very small quantities has a stimulating effect on the organisms, whereas in large amounts it has a detrimental effect. The results obtained *in vitro* suggest that the deleterious zone of the drug for the tubercle bacilli lies between the dilutions of 1:50,000 and 1:100,000.

The degenerated tubercle bacilli were still acid-fast and resembled young streptococci. It may not be out of place to remark at this point that the degenerated tubercle bacilli illustrated and described above must not be confused with the non-acid-fast granular forms of tubercle bacilli observed by Much (16) and Spengler (17) and confirmed by others (18), (19), (20), (21), because the Much granular forms are generally non-acid-fast and therefore do not stain a bright red with Ziehl-Neelsen stain, but do stain gram-positive.

In the instance in which the tubercle bacilli were planted on the surface of a cinchonized medium in dilutions up to 1:50,000 there was no actual growth; on the contrary, the beaded acid-fast forms illustrated above were the normal tubercle bacilli which underwent degeneration. The fact that the tubercle bacilli begin to degenerate in a dilution of 1:50,000 of quinine solution is very important, for, if we succeed in creating a cinchonized environment (in dilution 1:50,000) in the neighborhood of a tuberculous lesion, the growth of the tubercle bacillus would not only be inhibited, but the event would also cause the organism to degenerate and thereby help to build up the bodily resistance of the patient and give nature a chance to heal the lesions present.

Cahn-Bronner (22) who made an extensive study of quinine therapy in pneumonia was confronted with a similar problem; namely, how to create a proper concentration of quinine in the body and how to maintain it at

that level. He found that a dose of one gram of quinine per 10 kilos of body weight would be sufficient. Solis-Cohen (11), in treating pneumonia patients with quinine, suggested giving one gram of quinine intramuscularly as soon as the patient was seen and repeating the same dosage every three hours till the temperature remains below 102°F. Quinine is not employed to reduce the temperature, says Solis-Cohen, but to combat bacteria, bacterial poisons and tissue poisons.

Intramuscular administration of quinine is preferred by many investigators to oral and intravenous injections for several reasons. First, the subcutaneous or intramuscular injections form depots of quinine at the sites of injection, which maintain high concentrations of quinine in the blood for a longer period of time than any other administration. Second this method avoids the destruction of large quantities of quinine by the liver when it is taken by the gastrointestinal route.

According to Cahn-Bronner (22), when the quinine reaches the affected organs it is retained in them for a longer time than in the blood. The pneumonic lung, for instance, maintains, even after four days, the same concentration of quinine, which was the highest, while this drug was still circulating in the blood. The pneumonic patient excretes a small amount of quinine in his sputum for a long period of time.

Cahn-Bronner was fortunate to have had the opportunity to estimate the amount of quinine retained in the pneumonic as well as in the normal lungs of patients who suffered and died of pneumonia and who had been treated with quinine. He remarked that the amount of quinine obtained from the pathological lungs was much higher than that recovered from normal lungs. On the basis of these findings he suggested that the quinine was fixed in the pneumonic lungs for a longer time than in the normal lungs.

Boecker (23) found that when a tuberculous patient was given a dose of quinine intramuscularly a large quantity of quinine was found in the lungs and in the sputum. He also studied the amount of quinine deposited in the various organs of healthy guinea pigs which had been given quinine muriate subcutaneously. He noticed that a large percentage of this drug was deposited in the lungs. He therefore concluded that the lung tissue must possess a great affinity for quinine.

Hatcher and Weiss (24) made a special study of the distribution of the quinine in the various organs of the body after it was injected intravenously. They conducted their experiments on cats and dogs. They observed that about 95 per cent of an intravenous dose of quinine leaves

the blood circulation of the animals within five minutes and the greater part of this in two minutes. Moreover, when quinine is injected intravenously it is rapidly fixed in the capillaries from which as much as one-fourth of the total dose may be recovered by perfusion, if the animal is exsanguinated in a few minutes. The lungs, liver, heart and kidneys contained quinine in higher concentration than muscle or blood during the first two hours following injection.

Newton and Heine (14) treated 40 patients suffering from pulmonary tuberculosis with *transpulmin* (1 cc. of *transpulmin* contains 0.03 gm. of anhydrous basic quinine and 0.025 of camphor). The treatment consisted of intramuscular injections of 2 cc. *transpulmin* daily, for 3 to 5 weeks. Their records show very good results, although this treatment was more empirical than rational.

The results of these investigations, especially that of Boecker, confirm the findings of Cahn-Bronner. It is not impossible that the lung tissue has greater affinity for quinine, and hence the fixation of this drug in the lungs. However, the large amount of quinine found in the pathological lungs and especially in pneumonia may be explained on the basis of active hyperaemia, as reaction to infection set up in the lung tissue. The circulation being impaired at the inflamed area, the blood carrying the quinine is unable to circulate normally, and, therefore, greater absorption of quinine takes place. This also explains Boecker's finding in that large quantities of quinine were eliminated in the sputum.

CONCLUSIONS

The experiments on quinine *in vitro* demonstrated a definite effect of this drug on the tubercle bacillus. In a cinchonized medium up to 1:50,000 dilution, not only was the growth inhibited, but also the normal organism, originally planted on the medium, underwent a retrogressive change. However, in a similar medium, when quinine was only in 1:100,000 dilution, a luxuriant growth was obtained which excelled that of the control.

Tubercle bacilli, which were incubated in quinine solution of various dilutions first for 30 minutes, then for 120 minutes, showed a marked degree of growth inhibition. The higher the concentration of quinine and the longer the period of incubation, the greater was the effect.

The first experiment *in vivo* confirmed the latter part of the experiment *in vitro*. This was expressed by the gradual growth of the animal and the increase in body weight. Generally, the control set for the experi-

ment showed a comparatively poor increase in body weight, during the whole experiment.

In the second experiment *in vivo* conflicting results were obtained. Two out of three animals died from generalized tuberculosis in the early part of the experiment, while one animal, which received the same dose of tubercle bacilli and which was placed under the same treatment as the others, survived until the end of the experiment. Autopsy demonstrated no gross tuberculous lesions, except for a slight enlargement of the lymph nodes.

One can hardly tell whether the quinine treatment brought about the longevity of guinea pig 15, while the other two died from generalized tuberculosis. A repetition of this experiment in a larger number of animals with controls would be of great interest.

The third experiment *in vivo* showed that quinine administered to the animals offers some prophylactic measure against tuberculosis, and justifies more extensive experiments on a larger series of animals, from which, no doubt, we would be permitted to draw more definite conclusions. At present, since definite figures are at hand, it would be advisable to repeat the experiments with two or three checks in order to control some biological mishaps that may occur during the experiment.

Clinically, when degenerated tubercle bacilli are found in smears made from sputum, the prognosis may be good. The finding of degenerated organisms in the sputum may suggest an index for an increase in the bodily resistance of the patient, and that the number of the degenerated tubercle bacilli per slide or per field may be regarded as a gauge for the improvement of the patient's condition.

SUMMARY

1. A study of the effect of quinine on the tubercle bacillus is reported.

2. A pure culture of tubercle bacilli was planted on cinchonized glycerin-agar medium in dilution ranging from 1:10 to 1:100,000, with the following results: The growth of the tubercle bacillus was inhibited in dilutions up to 1:50,000, but was luxuriant at 1:100,000. The tubercle bacilli underwent retrogressive changes in dilutions up to 1:50,000, but were normal in 1:100,000 dilutions.

3. The tubercle bacilli were incubated first for 30 minutes and then for 120 minutes in quinine solutions of various dilutions. Tubes were inoculated with the microörganisms so treated. The longer the period of incubation and the higher the quinine concentration the greater was the effect.

4. The microörganisms were exposed to quinine solution as above and then injected into guinea pigs. It was noted that, the higher the concentration of the quinine solution and the longer the period of exposure, the higher was the body weight at the termination of the experiment.

5. Animals were treated for 3 weeks with quinine and then inoculated with a large dose of tubercle bacilli. These animals lived longer and their body weights were much higher than in those which were first injected with the same dose of tubercle bacilli and in which the quinine treatment did not start till three weeks later.

The author desires to express his appreciation to Dr. H. C. Sweany for assistance in planning the experiments and in the preparation of the illustrations, to Miss Grant for help in planning the diet for the animals during the experiment, and to other members of the staff for their aid in carrying out the experiments.

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FIG. 1. This shows samples of tubes of different quinine dilutions and the rate of growth three months after inoculation. No growth was present on any of the tubes up to 1:50,000. A whitish precipitate was found on the surface of all slants 1:10, attributed to reaction between quinine and tubercle bacilli implanted on slants. Luxuriant growth was found on all tubes 1:100,000 quinine dilutions.

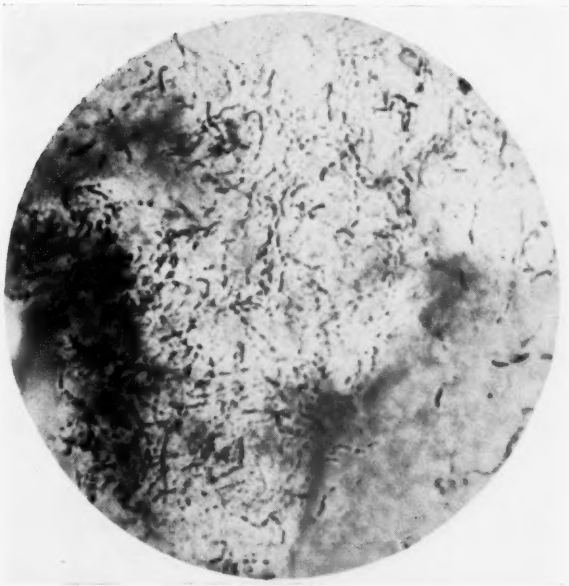

FIG. 2. Smear from tube 1:50,000 quinine dilution in the medium. Note streptococcic arrangement of degenerated tubercle bacilli.

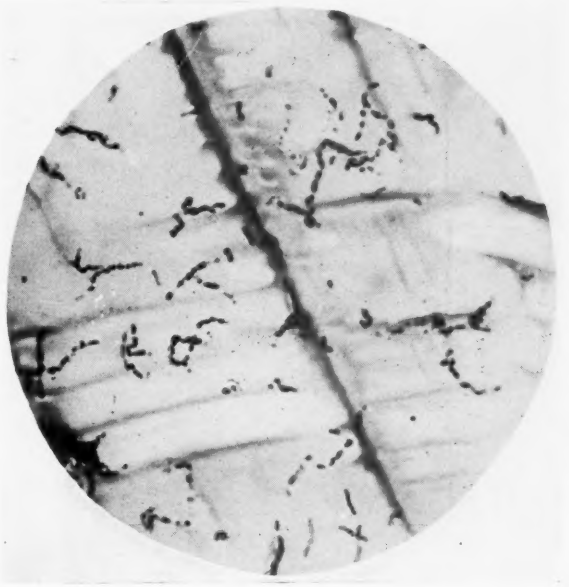

FIG. 3. Smear from tube 1:10 quinine dilution in the medium. Note the degeneration of the tubercle bacilli.

FIG. 4. Smear from tube 1:100,000 quinine dilution in the medium. Note the normal tubercle bacilli in contrast with fig. 2.

FIG. 5. Smear from tube "control." No quinine in the medium. Compare this with figs. 2 and 3.

FIG. 6. Series I. Photograph presents the rate of growth of microörganisms at the end of 15 days. Note bacteriostatic effect of quinine up to 1:5,000, after 30 minutes of incubation in quinine solutions.

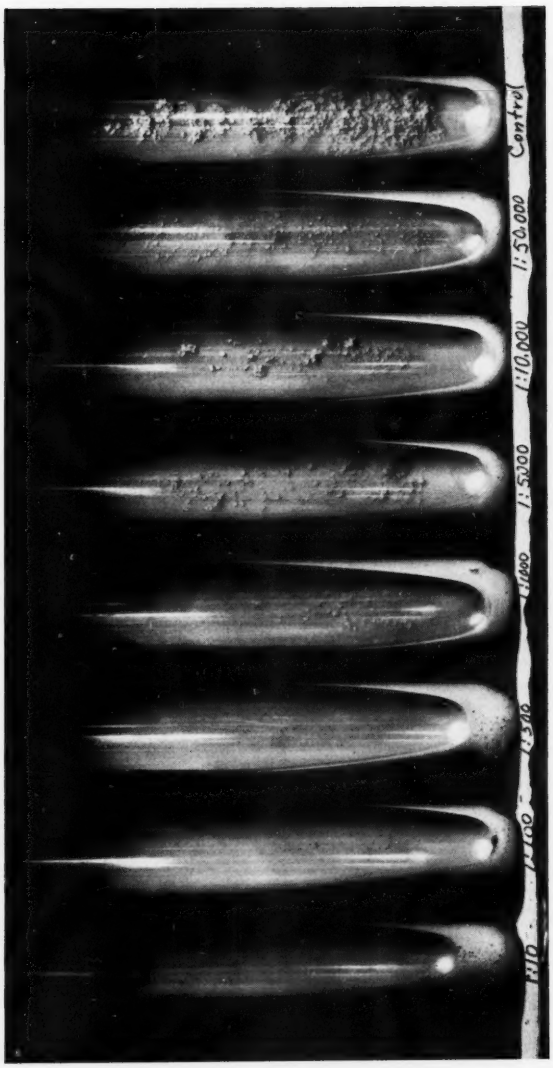

FIG. 7. Series II. Photograph presents the rate of growth of tubercle bacilli at end of 15 days. Note bactericidal effect of quinine in dilutions up to 1:500 and bacteriostatic effect up to 1:10,000, after exposure of 120 minutes.

COMPLEMENT FIXATION WITH URINE IN TUBERCULOSIS[1]

MARIAN E. PARKER

In the vast array of diagnostic procedures for the detection of tuberculous foci, several methods have been based upon the theory that specific antibodies and bacillary-disintegration products are found in the blood and urine, whenever there is an active tuberculous lesion in the body.

Marmorek (2) believed that a toxin is found in the urine in active tuberculosis and he evolved a method for its detection by complement fixation. He demonstrated this toxin in the filtered urine, using the serum from immunized horses as a carrier of the specific antibody. The tests agreed with clinical findings and with simultaneous complement fixation on blood sera in 95 per cent of his cases. Debré and Paraf (3) used a similar test and concluded that the detection of the antigen in the urine is indicative of an active lesion in the urinary system. Fried (1) attempted to confirm their findings, but concluded that there is no antigen in the urine of patients with active tuberculosis detectable by complement fixation. Takahata (4) believed, however, that a positive complement-fixation test indicates a genitourinary lesion, regardless of active lesions anywhere else in the body. Merz (5) asserted that it is specific, if pulmonary tuberculosis can be eliminated.

Apparently stimulated by Marmorek's work, Wildbolz (6) concentrated the urines of tuberculous patients and inoculated the concentrates into the skin of their respective donors. He maintained that a positive reaction invariably indicates activity of a lesion, but Lewis (6) concluded that a positive reaction may be caused by chemically irritating substances in concentrated urine. According to Korns (8), the test is not specific or practical, and Hayman (7) believed that it is liable to errors but that, in general, it corroborates the clinical diagnosis.

In an attempt to confirm or negate these conflicting findings, 373 complement-fixation tests were performed on the urines of 291 patients, 38 tests on 38 normal individuals, 48 tests on 48 patients having either

[1] From the Wm. H. Maybury Sanatorium, Detroit Municipal Tuberculosis Sanatorium, Northville, Michigan.

scarlet fever or measles, and 24 tests on 24 pregnant women, making a total of 483 tests on 401 individuals.

TECHNIQUE

The technique used was a modification of the Kolmer modification of the Wassermann complement-fixation test. For the preparation of the antigen, tubercle bacilli from thirty different strains were dried to constant weight, pulverized and carefully triturated with physiological saline solution, in such quantity that each cubic centimetre of saline contained 10 mgm. of bacilli. An antiserum was prepared by injecting rabbits intravenously with increasing doses of antigen, from 0.2 to 1 cc. at five-day intervals, until titration of blood serum from the animals showed the presence of a sufficient concentration of complement-fixing antibodies. The anticomplementary unit of the antigen was 0.04 cc.; for all further tests, 0.5 cc. of a 1:25 dilution was used. The antigenic unit of the antiserum, titrated against the above amount of antigen, was 0.001 to 0.0025 cc. For the tests 0.5 cc. of a 1:100 dilution was used. Complement, sheep cells, and haemolysin were prepared and employed according to the Kolmer technique. A number of urines were used in preliminary tests to determine the most satisfactory state of urine for complement fixation. Some specimens were centrifugated and the supernatant fluid used. To others was added tenth-normal sodium hydroxide to alkalinize the urines slightly, and to some a small amount of dilute hydrochloric acid to acidify them. In order to neutralize others, the buffer solution of phosphates was used as in blood-urea determinations. It was finally determined that an uncentrifugated, neutral urine was best, and 0.2 cc. of urea buffer solution was added to 4 cc. of urine for each test. The amount of urine used was 0.5 cc., 0.25 cc., 0.1 cc. These were titrated for antigen with the rabbit antiserum, and for antibodies with the bacillary suspension, using controls in each case.

RESULTS

The results of the 483 complement-fixation tests for tuberculosis on urines are summarized in table 1.

In order to correlate results of the tests with pathological findings, the postmortem urines and kidneys of 15 patients who died of pulmonary tuberculosis were studied. Each kidney was sectioned into thin slices and searched for evidence of tuberculosis. Histological studies were made of any area which appeared suspicious, but upon which a definite

TABLE 1

	TOTAL NUMBER OF TESTS	POSITIVE RESULTS FOR						TOTAL POSITIVE RESULTS		NEGATIVE RESULTS		ANTICOMPLEMENTARY	
		Antigen and antibody		Antigen		Antibody							
	Number	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Active pulmonary tuberculosis*	311	41	13.1	4	1.2	83	26.6	128	41.1	170	54.6	13	4.1
Inactive pulmonary tuberculosis	62	4	6.4	3	4.8	16	25.8	23	37	36	58.1	3	4.8
Renal tuberculosis†	24	6	25	1	4.1	7	29.1	14	58.3	10	41.6		
Normal individuals	38									38	100		
Nontuberculous patients	72			2	2.7	3	4.1	5	6.9	67	93		
Positive urinary findings:													
1. Albumin	82	10	12.1	1	1.2	23	28	34	41.1	45	54.8	3	3.6
2. Leucocytes	61	10	16.4	1	1.6	24	39.3	35	57.3	23	37.7	3	4.9
3. Erythrocytes	80	8	10			21	26.2	29	36.2	47	58.7	4	5
4. Casts	42	5	11.9	1	2.8	11	25.2	17	40.3	23	54.7	2	4.7

* The criteria for active pulmonary tuberculosis were positive sputum or fever at any time during the patient's stay in the Sanatorium.

† The diagnosis of renal tuberculosis was made on the basis of positive culture and guinea-pig inoculation of urines.

diagnosis could not be made grossly. Tubercles in the kidneys were found in only four cases. Of these four, the postmortem urine was negative in one case, anticomplementary in two, and positive for antibodies in one. Of the 11 cases in which there were no demonstrable tubercles, 8 urines were negative and 3 anticomplementary. In other words, the urine from those kidneys which were apparently free from tuberculous lesions gave negative tests. In those in which tubercles were demonstrated, 50 per cent were anticomplementary, 25 per cent were negative, and 25 per cent were positive for antibodies.

DISCUSSION

In the series of complement-fixation tests on urines for the detection of tuberculosis, the greatest percentage of positive results (58.3) was found in cases of demonstrated renal tuberculosis. Practically the same percentage (57.3) was found in those urines showing many leucocytes. Then, in decreasing percentages, positive tests occurred in 41.4 per cent of urines containing albumin, 41.1 per cent of urines of patients with active pulmonary tuberculosis, 40.3 per cent of urines showing casts, 37 per cent of urines of patients with inactive pulmonary tuberculosis, 36.2 per cent of urines containing erythrocytes, 6.9 per cent of urines of nontuberculous patients, and finally no positive results on urines of normal individuals. In other words, there is a downward curve of positive results found, ranging from over 50 per cent in renal lesions to zero per cent in apparently normal individuals. It is evident, from this observation, that the test is fairly specific for tuberculosis. Moreover, since the number of positive results in renal tuberculosis closely parallels the results found in pyuria (one of the most frequent urinary findings in renal tuberculosis), it indicates a tendency to demonstrate renal lesions. The presence of active or inactive pulmonary tuberculosis does not apparently affect the results, since 41.1 per cent positive results are obtained in active lesions, and 37 per cent in inactive ones.

The 6.9 per cent of positive results in nontuberculous individuals compares rather favorably with the percentage of false positive findings in other complement-fixation procedures. When one considers that this test is performed on urine, a complex body fluid, with extraneous factors such as urinary salts which may disturb complement fixation, it portends the possibility of greater accuracy in the future, if those factors can be determined and eliminated.

One is impressed by the number (45 out of 373) of tests in which both

antibodies and antigen were present. Since it must be assumed that in any so called specific serological reaction only free antigen or free antibody can be demonstrated, the simultaneous occurrence of both should probably be explained by the multiplicity of antigens which have been shown to exist as serologically specific units in the bacillus. It may be possible that in those urines in which both tests yielded positive results, heterologous antigen and antibodies existed side by side, particularly since the antigen used contained all possible fractions of the bacillus.

The attempt to correlate the urinary findings with the pathological lesions in 15 cases was disappointing. The large number of anticomplementary tests (5 out of 15) on the postmortem urines may be explained by the fact that the tests were not performed immediately on these urines, and disturbing factors, such as chemical changes in the urine, may have occurred. On all other urines, tests were made at once. The finding of only one positive result for antibodies, in spite of demonstrated renal lesions at autopsy, in 4 cases, precludes the possibility of considering this test a specific one for genitourinary tuberculosis.

SUMMARY AND CONCLUSIONS

Four hundred and eighty-three complement-fixation tests for the detection of tuberculosis were performed on urines of tuberculous and nontuberculous individuals. The results were compared with clinical findings in each case. From 15 autopsies the kidneys were studied for tuberculous lesions and complement-fixation tests were done on the postmortem urines.

The conclusions are:

1. The presence of specific antigens or antibodies in the urine, as demonstrated by complement fixation, is highly indicative of a tuberculous lesion somewhere in the body, but not necessarily in the urinary system.

2. A negative test has no diagnostic significance.

I wish to express my indebtedness to Miss Sophie Levine and Mrs. Marie Voldrich for technical assistance.

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